Review Article

Quantum dots: The trailblazers of early detection

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Abstract

Considering the robust awareness of early detection among oral clinicians and patients the increasing imposition of better methods for screening of oral precancerous/cancerous lesions has become imperative. Although histopathology has been considered the indispensable gold standard, it has its pros and cons, as sometimes the diagnosis is compromised with the variabilities subject to the histopathologist under concern. In the realm of oral healthcare, one pioneering trailblazer is making waves, which are 'quantum dots'. Quantum dots are poised to transform the landscape of oral precancer and cancer screening. These nano-sized semiconductor particles possess extraordinary properties that set them apart from conventional detection methods. Their ability to emit distinct wavelengths of light when excited makes them ideal candidates for early detection. The keywords were pitched in and the research literature from the last 15 years (2008-2022) was extirpated to find out the information that existed, the discrepancies and the void left for upcoming research. Its nature and ingenuity have given rise to a transformative approach that holds the potential to redefine the future of oral healthcare. With each breakthrough, we edge closer to a world where the early detection of oral precancerous/cancerous lesions becomes the norm rather than the exception.

Keywords: Early detection, literature review, nanotechnology, oral precancerous lesions oral cancer, original research, PubMed indexed, quantum dots, Scopus indexed, web of science indexed

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INTRODUCTION

The gold standard procedure for detection is a conventional oral examination with histopathological analysis which lacks accuracy in the detection of molecular changes and is susceptible to diversified interpretation.[1] Determination of the efficacy of therapy and monitoring recurrence, which are highly sensitive and bio-specific are the needs of the hour.[2] Quantum dot imaging probes are semiconductor nanocrystals that are an essential tool especially for multiplexed, quantitative, precise, and long-term fluorescence imaging and detection.[3] Quantum dots might be able to satisfy the requirements even though research into them is still in its early phases.

MATERIALS AND METHODS

A web-based search was performed via Google Scholar, PubMed database, and Web of Science with keywords - nanoparticles in oral cancer, quantum dots, nanotechnology, early detection, oral potentially malignant disorders, and oral precancerous lesions. The other keywords used were diagnosis, therapy, tumour microenvironment, oral microbiome, molecular alterations,

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biosensor, bioconjugation, and imaging. Original research studies, reviews, and case reports published from 2008 to 2022 were included to conduct this review of literature starting from its inception to the developments of recent times, loopholes, and suggestions of its future prospects.

DISCUSSION

Brief introduction of quantum dots

Quantum Dots as elucidated by Zhang H, Yee D, and Wang C 2008 are semiconductor nanocrystals that possess quantum confinement properties. Upon excitation, it emits fluorescence from the visible spectrum range to the infrared region. A single quantum dot consists of 100–100,000 atoms in one unit of a crystal. Within the nanometer scale, it ranges between 2–10 nm.[2]

Chemically, they are divided based on their placement in the periodic table. We have Category I hailing from Group III–V and then the second category, potentially more hazardous, belonging to II-VI that releases heavy elements.[4] Cadmium Selenide (CdSe) is the most widely used component as quantum dots wherein the core belongs to CdSe but the outer shell is of zinc sulphide (ZnS).

The energy band gap that is a constant and integral component in bulk semiconductors, stems from the unique composition of their materials. As the semiconductor crystal is scaled down below the Bohr radius, electronic excitation states undergo energy level shifts, responding to particle boundaries in fascinating ways.[5] Bohr radius is a physical constant that defines the most probable distance between a hydrogen atom's nucleus and its electron in the ground state. Its precise value is a mesmerizing 5.29177210903 (80) ×10 − 11 m.[6]

Traditional imaging and the scarcity of suitable fluorescent markers pose quite a challenge. These semiconductor nanoparticles with their unique photophysical properties, have the potential to be remarkable fluorophores for *in vivo* fluorescence imaging, overcoming the shortcomings of those traditional dyes.[7] Thus, the increased thickness of the shell of CdSe, along with the emission of the wavelength of light that ranges between visible light and the infrared region has been quite beneficial for biological applications. Therefore, the explicit study of quantum dots in oral precancerous and cancerous lesions could be a boon in early detection.

Quantum dots in bioimaging

After overcoming the difficulty of obtaining biocompatible nanocrystals, early detection with quantum dots has been the subject of extensive research.[7] Dubertret, P. Skourides, *et al.* demonstrated its ability to completely transform biological imaging as early as 2002.[8] Active targeting of cancer antigens in imaging probes has gained a lot of attention due to its potential to identify early-stage malignancies and associated metastases.[7] Quantum dots were known to enhance molecular and cellular level diagnostics and amplify ultrasensitive bioassays.[7]

When associated with biomarkers it was detected that the quantum dots-based methodology is more sensitive, accurate, and economical than traditional immunohistochemistry. Its novelty was quite worthwhile, particularly in developing nations, where the survival window is quite low due to socioeconomic status.[8] Gao *et al.* 2007[9] established the importance of quantum dots in determining the status of metastasis by binding antibodies with them, which reduces binding activities giving full-length coverage of the antibody. Yong *et al.* used non-cadmium-based quantum dots and therapeutic efficacy was diagnosed in the form of non-toxic optical probes to study live cancer cells.[10]

Regarding tissue penetration in lymph node metastasis, quantum dots exhibited promising results portrayed by L. A. Bentolila, Y. Ebenstein *et al.* 2009.[11] and K.-T. Yong, I. Roy, H. Ding *et al.* 2009.[12] Kobayashi *et al.* 2009 studied lymph node metastasis by using melanoma cells labelled with quantum dots, which significantly showed its worth in detecting the lymphatics.[13] The rationale behind the benefit of Quantum Dots on multimodal imaging and cancer mapping was cited in the paper by Tan A, Yildirimer L, Rajadas J *et al.* 2011. They cited that quantum dots have the ability of size-tuneable fluorescence and their range expanding from the ultraviolet to the near-infrared regions with the larger diameters fluorescing in red and the ones with smaller diameters in blue.[5]

Quantum dots in the realm of oral and maxillofacial pathology

Oral biomarkers

As per Harris *et al.* 2007[14] who were quoted by Jokerst JV *et al.* 2009[15] the current methods of practice which included ELISA suggested to be not multifaceted. A similar article by Bhasin *et al.* 2008[16] states that it is challenging to accurately assess initially because biomarker concentrations are mildly altered. As the current screening methods have limits of detection being quite close to the diagnostic values that provide differential in clinical categories[16] precision in final diagnosis becomes very concerning.

Jokerst JV *et al.* 2009 cite in their paper that physicians advise frequent screenings regularly to detect cancer at the

earliest. Current test designs are expensive and arduous and thus require intrusive sampling methods. In the case of quantum dots a smaller sample size, economic costs, and brief analytical span became an asset to the prevention at the point of care to hone its ability to complex multifaceted analysis.[15] Supportive literature by Mandel *et al.* 1993[17] and Malamud *et al.* 2006[18] states that saliva mimics human oral and systemic conditions by releasing the biomarkers and the components of the serum proteomics, which could be bio-conjugated with quantum dots and aid in early detection.

Oral probes for early detection

Ranging from 5–20 nm these nanoparticles constitute a CdSe core with a ZnS coat followed by a polymer passivation coat[19] by polyethylene glycol.[20] Various applications in the macro and micro size regimes have found quantum dots to be quite useful as qualitative and quantitative probes due to their long-term photostability, strong intensity, size-tuneable narrow emission profile, and broad UV excitation spectrum. Despite this Soper *et al.* 2006 addressed the difficulty of no available uniform method for connecting quantum dots to bioligands for point-of-care diagnostics and prognostics. Nano biochip sensors were mentioned which were eventually devised to cater for analysis at the point of care.[21]

Quantum dots as nano biochip for early precision in diagnosis

The nano biochip ensemble separates and measures biological analytes from complex matrices in a closed and tiny system (chip) using fluorescent transduction signals from nanoparticles and a size-tuneable nano-net embedded in agarose microspheres. These tiny sensor devices are ideally suited for the analysis of complex fluids, such as oral samples because their performance metrics correlate positively with established gold standard macroscopic analytical techniques.[21]

Jokerst JV *et al.* 2009 cited in their research literature that quantum dots were incorporated with such a nano biochip to analyze three of many important biomarkers in oncology which were – CEA, CA125, and C-erbB2. The three of them eventually found significance in oral cancer, which was mentioned respectively by Rajguru JP, Mouneshkumar C, *et al.* 2020 for CEA,[22] Balan JJ, Rao RS, Premalatha BR *et al.* 2012[23] for CA 125 and Meng Y, Yang P, Ma L 2020[24] for C-erbB2.

Comparison of quantum dots with other conventional fluorescence study methods

Insight into the literature by Zhao JJ *et al.* 2011[25] informs us that the authors had researched the comparative analysis between quantum dots and fluorescein isothiocyanate labelling technique in Tca8113 (tongue squamous cell carcinoma) cell lines. They aimed to study the fluorescence and the photostability of the mentioned methodologies. The fluorescence signal was quite strong which came from the quantum dots that were undeterred and strong, unlike the one from the fluorescein isothiocyanate technique.[25] This study was the first original research that was conducted utilizing quantum dots in oral carcinoma (tongue squamous cell carcinoma). The major negative drawback was it did not discuss the cost-effectiveness, sensitivity, specificity, and reproducibility in real-time. Nor did it hint at the feasibility of utilizing quantum dots in determining the oral precancers or oral carcinoma from other oral mucosal sites.

Quantum dots in growth factors

The literature review by Banu Virupakshappa 2012[26] caters to these unanswered queries mentioned above, by stating in their article that gold nanorods were used to selectively and sensitively target the UM-A9 antibodies. It was specific to the detection of squamous cell carcinoma of the head and neck region, precisely the early detection of oral cancer. It was stated that real-time imaging and tracking of molecules in living cells can be done with antibodies conjugated with quantum dots which could have high sensitivity and resolution.[26] Quantum dots were able to be conjugated with oral cancer-specific antigen epidermal growth factor receptor (EGFR) and aid in the early detection of oral cancer.[26]

Quantum dots as nanowires, nano-biochips, and bioassays for early precisive detection

Banu Virupakshappa 2012[26] answered the queries unattended by Zhao JJ *et al.* 2011 which stated that not only quantum dots are able to produce exceptional quality images of the tumour sites because of size tuneable emissions, but they are quite brighter than the organic dyes and economic than most contrast media currently in use since one light source is used for excitation. Sensors engraved with nanowires could detect proteins and biomarkers with a few drops of patient blood. The lab-on-chip (nano biochip) technology was quite efficient using methods that would, encourage early screening and diagnosis during dental visits. It included miniaturized, integrated, automated, disposable microfluidic cassettes, and affordable diagnostic devices with pre-loaded, freeze-dried reagents and utilized in conjunction with a hand-held tool.[26]

The nano biochip/lab on chip takes cytology samples obtained via brush biopsy and places them in a chip which is further inserted into an analyser providing the results in 15 minutes.[26] The raised questions about the toxic

elements as the cytotoxicity levels needed to be addressed so that to get more precision we are not resorting to any unethical means.[26] Although it was hypothesized that both premalignant and malignant lesions might be taken care of via this methodology,[26] the question remains how effectively would it be able to detect the malignancy transformation potential of oral precancerous lesions and the prognostic directions of obvious clinically visible malignant oral lesions in the future.

Alok A, Kishore M, Panat S *et al.* 2013[27] cited in their literature the gravity of quantum dots to evaluate cell motility assay (bioassay) to distinguish between invasive and non-invasive cell lines. The intriguing concept of bio barcode amplification was put forth that used colloidal gold nanoparticles conjugated with target DNA and magnetic microbeads, which were evaluated by colorimetric method.[27] This gave a window to study the intricacies of oral cancer at a much molecular depth but failed to provide the background about its technique sensitivity and specificity. To elevate the entire process of bio barcode amplification high-end infrastructure might be needed, because of this negative aspect it was never discussed in the future literature.

Quantum dots in nano vaccines for oral cancer

Cancer nano vaccines were introduced to induce humoral and cellular immunity making individuals immune,[27] although implantation in oral oncology was still unexplored. Surface chemistry is considered an important factor since the entire evaluation depends on how well the quantum dots get conjugated with target DNA/molecules/antibody/cell lines.[27]

Cytotoxicity levels and optical imaging with quantum dots

Authors[27] shed light on the questionable biocompatibility, ease of availability, and most importantly the cost of infrastructure which keeps on lingering even after years of studying and tremendous research on nanoparticles in the field of oral oncology. Chen XJ, Zhang XQ, Liu Q, Zhang *et al.* 2018[28] discuss the usage of nano contrast agents in oral cancer. A combination of folate pre-conjugated chitosan and magnetic poly (lactide co glycolide) PLGA nanoparticles to be used as MRI contrast agents serve as better contrast agents due to the shortening of T2 relaxation time and enhancement of the nanoparticles. The cytotoxicity levels were improved by the uptake of the nanoparticles by the folate receptor-positive KB cell lines. Optical coherence tomography was conducted utilizing gold nanoparticles which aid in greater penetration depth in determining oral carcinogenesis and a better contrast in oral epithelial dysplasia which was cited to be successful in the hamster model.[28]

Use of quantum dots as nanosensors in lymphatic analysis

Gold nanoparticles in the form of molecularly activated plasmonic nanosensors have been known to accentuate the findings of sentinel node biopsy analysis in oral cancer resection.[28] Anti-EGFR antibodies conjugated with gold nanoparticles were known to exhibit 600% more affinity towards detecting oral malignant epithelial cells along with high optic signals in surface plasmon resonance scattering.[28] In the case of Raman scattering, it was observed that nanoparticles accentuated it, within saliva samples in oral cancer patients[28] which might be of great potential in early detection.

Quantum dots in periodontal health

Although in none of the previously mentioned scientific literature human models were dealt with, mostly all the evaluation was conducted on murine/hamster models leaving a few of them like Zhao JJ *et al.* 2011 who dealt with tongue cancer in humans cell lines. Liang G, Shi H, Qi Y, Li J *et al.* 2020[29] first mention increased efficacy in periodontitis by conjugating nanoparticles and antibacterial drugs such as tinidazole/metronidazole, which was able to penetrate the porphyromonous gingivalis biofilm. It was quite a new benchmark in the field of oral and maxillofacial pathology, that beyond oral oncology nanoparticles were able to make a name and have some conclusive results.

Quantum dots as nanorobots with targeted action

The role of nanorobots, which release downregulators, inhibitors, and antagonists within the pyrogenic pathway. They take up the endogenic pyrogens in a targeted way and after chemical alteration, they release them in an inactive form into the body.[30]

Other aspects of quantum dots in oral and maxillofacial pathology

Quantum Dots in the form of nanoparticles were classified into different genres of dental treatment and specialties of dentistry. Apart from nano biosensors and saliva nano biochips and nanodevices, the importance of quantum dots was discussed in nanoelectromechanical systems in oral cancer diagnosis, nano vectors in gene therapy, and nano stem cell systems in tissue engineering in the realm of oral and maxillofacial pathology.[31]

Devising immunosensors and detection of inflammatory cytokines

Another fascinating breakthrough was cited[32] wherein DNA-templated Quantum Dots was used as electrochemical reporters to detect interleukin 8, a potent pro-inflammatory cytokine to detect oral cancer. The highlight of this method

was its selectivity, reproducibility, and applicability in serum samples as well. It aids in incorporating quantum dot conjugated DNA templates in a facile way, avoids the arduous protocol of antibody conjugation, and makes it feasible for other protein biomarkers that facilitate effective biosensing designs.[32] Quantum dots were discussed in the efficacies of engineering immunosensors with gold electrodes which were constituted by cysteamine and glutaraldehyde named Cys-GA-anti-Cyfra21.1 antigen/AuE. The study claimed that this immunosensor was able to detect Cyfra21.1 biomarker in a much more appropriate and practically viable way in unprocessed saliva which might detect oral abnormalities.[33]

Use of quantum dots in nano enzymes

Recently nanozymes were cited which might be a game-changer in the early detection and assessment of the tumour microenvironment, tissue imaging, analysis of the oral cancer microbiome, and tumour microenvironment.[34] Since 2002[8] nanotechnologies have influenced, modified, altered, and redesigned the whole aspect of early detection significantly. Some were conducted on animal models and the rest used human specimen (blood/serum/saliva). Usage of antibody-conjugated methods to nano enzymes, and quantum dots have come a long way in oral and maxillofacial pathology.[8]

The future of early detection in oral and maxillofacial pathology via nano-route

Despite extensive research on nanomedicines and nanotechnology, the net quantifiable results are yet a long way to be actualised in a much more technique-friendly and economical way. Since its inception in oral and maxillofacial pathology, significant synthetic techniques and strategies have been adapted to enhance its features. Bioimaging was the primary arena that was explored, further extending into providing immunity via nano vaccines, detecting different inflammatory cytokines, molecular and cellular level biomarkers pathognomonic for oral cancer and oral epithelial dysplasia.

The utilisation of quantum dots in oral and maxillofacial pathology will promulgate much more precision, efficacy, sensitivity, and specificity in the early detection of oral cancer and oral epithelial dysplasia. The survival rate might improve in oral cancer-affected individuals and give them a better quality of life since metastasis might be evaluated using such nanotechnology. Improving the surface coating of these semiconductors is a must since most assessments are impossible without bioconjugation.

Its biotoxicity levels need to be addressed, since in the past only one literature[33] discussed the reduction of its cytotoxicity using KB cancer cell line folate positive receptor.[33] Although the concept provided seems quite arduous, technique sensitive, exorbitant, and difficult to manoeuvre. The research on the prospects of quantum dots needs to be explored more in developing nations, specifically India. India has a significant burden of oral cancer as the morbidity and mortality are quite severe, as the disease often gets detected at an advanced stage.[35] Last but not least more conclusive studies need to be conducted on oral precancerous lesions to prevent cancerous transformation.

CONCLUSION

Most such research was conducted in developed nations such as Japan and China. Significant research literature came from American universities with just one literature[33] from Iran among the developing nations. It is a true reflection of where we stand in the field of quantum dots in the realm of oral and maxillofacial pathology. The right measures that need to be taken are making it more technique-friendly, lowering cytotoxicity levels, amplifying its bioavailability, making it more affordable and widespread amidst common mass, better biomodulation for better bioconjugation, good collaboration across multiple disciplines is going to spearhead the quality of oral epithelial dysplasia oral cancer and treatment in leaps and bounds. Thus, we suggest that quantum dots due to their various unique physical properties might evolve to be a trailblazer in this rising burden of oral cancer in the Indian population and give precisive diagnosis in oral epithelial dysplasia as well thus preventing a possible malignancy transformation at a very earlier stage.

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Conflicts of interest

There are no conflicts of interest.

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