

Quantum Dots for Margin Visualization in Non-Melanoma Skin Cancers: Advances in Nanotechnology for Cutaneous Surgical Precision

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Abstract

Background: Non-melanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma, are the most prevalent malignancies worldwide. Achieving histologically clear margins is critical for recurrence prevention, yet conventional techniques often fall short in precision and real-time intraoperative guidance.

Objective: To evaluate quantum dots as emerging nanotechnology platforms for surgical margin visualization in NMSC, highlighting their physicochemical properties, targeting strategies, imaging modalities, safety profiles, and translational barriers.

Methods: A comprehensive review of literature from 2011 to 2025 was conducted, encompassing quantum dot design, bioconjugation techniques, tumor-targeting ligands, imaging integration with dermatoscopes and microscopy, and preclinical/clinical applications in cutaneous oncology.

Results: Quantum dot-based systems offer unprecedented spatial resolution (as low as 20–100 μm) for tumor margin delineation due to their exceptional brightness, photostability, and multiplexing capability. Functionalized quantum dots targeting biomarkers such as EGFR and integrins ($\alpha\text{v}\beta3$, $\alpha\text{v}\beta6$) demonstrate tumor-specific accumulation both in vivo and ex vivo. Comparative studies show that quantum dots outperform traditional dyes like ICG in photostability and specificity. Biodegradable alternatives, including carbon, silicon, and CuInSe-based quantum dots, are mitigating toxicity concerns. Integration with time-gated imaging, AI-assisted classification, and real-time surgical guidance systems further enhances clinical utility.

Conclusion: Quantum dots represent a transformative innovation in the precision resection of non-melanoma skin cancers. While challenges remain in safety, delivery, and regulatory approval, ongoing advancements in biocompatibility and intelligent imaging integration position quantum dots as pivotal tools for the next generation of fluorescence-guided dermatologic surgery.

Keywords: Quantum Dots, Non-Melanoma Skin Cancer, Surgical Margin Visualization, Fluorescence-Guided Surgery, EGFR Targeting, Nanotechnology, Multiplex Imaging, Cutaneous Oncology, Bioconjugation

1. Introduction

Non-melanoma skin cancers (NMSCs), primarily basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), constitute over 95% of all skin cancers and are the most commonly diagnosed malignancies worldwide [1]. While BCC is typically indolent, SCC carries a higher risk of local invasion and metastasis, with rising incidence projections across aging and sun-exposed populations [1,2]. The primary treatment for NMSC remains surgical excision, where complete removal with histologically negative margins is critical for curative outcomes. Despite

advances in surgical dermatology, margin delineation during excision remains challenging. Conventional approaches such as frozen section analysis, dermoscopy, and Mohs micrographic surgery (MMS) offer varying levels of precision but suffer from drawbacks including sampling errors, procedural complexity, high costs, or limited intraoperative visualization [3,4]. There is an unmet need for real-time, high-resolution tools that can reliably highlight tumor borders during excision, especially in cosmetically and functionally sensitive areas. Quantum dots (QDs), semiconductor nanocrystals with tunable fluorescence, represent a

transformative platform for surgical margin visualization. Their unique optical characteristics include size-dependent emission wavelengths, high quantum yield, narrow emission spectra, broad excitation profiles, and exceptional photostability [5,6]. These properties allow for deep tissue penetration using near-infrared (NIR) fluorescence, multiplex imaging of tumor markers, and minimized background autofluorescence, features particularly advantageous for intraoperative guidance in cutaneous oncology (Figure 1). In the context of NMSC, QDs can be functionalized with monoclonal antibodies, peptides (e.g., RGD or A20FMDV2), or aptamers targeting overexpressed biomarkers such as EGFR, $\alpha\beta3$, and $\alpha\beta6$ integrins [7-10]. These conjugates enable real-time fluorescent labeling of tumor margins, even within complex tissue environments or 3D tumor spheroids [11]. Furthermore, innovations in QD delivery, such as microneedles, stem cell vehicles, and liposomal encapsulation, enhance tumor selectivity while minimizing systemic exposure [12,13]. Emerging preclinical evidence now supports the feasibility of QD-guided margin

visualization in NMSC, offering spatial resolution in the range of 20–100 μm [3,4]. This review synthesizes current data on QD formulations, targeting ligands, delivery strategies, and clinical translation potential, and highlights how QDs may improve intraoperative precision and long-term oncologic outcomes in cutaneous oncology.

Schematic illustration of a quantum dot (QD) platform for surgical margin visualization in non-melanoma skin cancers. QDs (e.g., CdSe/ZnS, InP/ZnS) are surface-functionalized with ligands such as EGFR monoclonal antibodies, RGD peptides, or A20 peptides for selective binding to tumor-associated markers. These nanoconjugates can be delivered via intravenous injection, mesenchymal stem cell carriers, or microneedle arrays. Upon binding to tumor margins, QDs emit near-infrared (NIR) fluorescence, enabling real-time intraoperative guidance and precision excision.

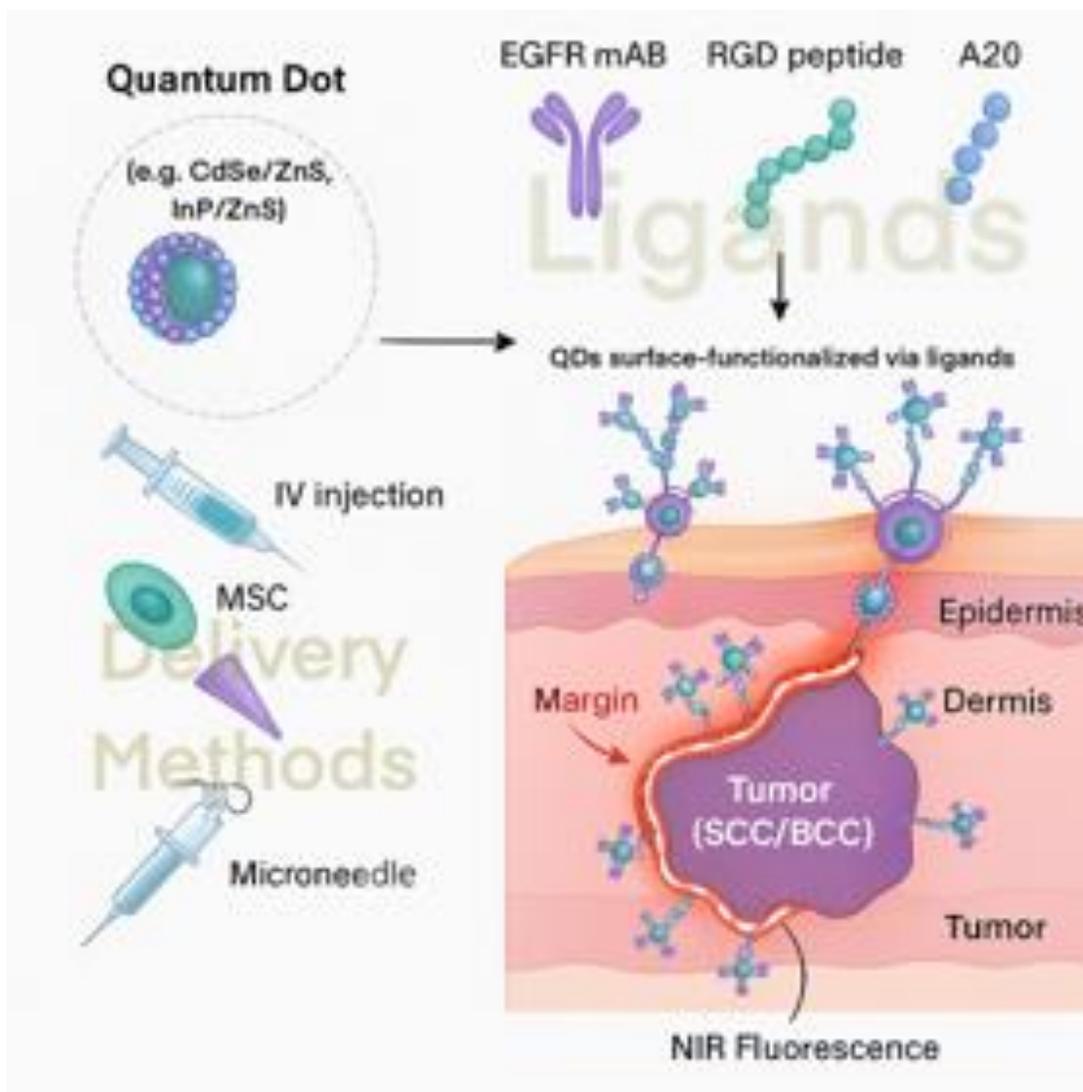


Figure 1: Mechanism of Quantum Dot–Mediated Tumor Margin Visualization

2. Physicochemical Properties of Quantum Dots

QDs are semiconductor nanocrystals, typically ranging from 2 to 10 nanometers in diameter, whose optical and electronic properties are dictated by their size and composition. Their design can be customized to meet the demanding requirements of surgical oncology, especially for real-time, high-contrast visualization of non-melanoma skin cancer (NMSC) margins.

2.1. Composition and Core–Shell Architecture

Most QDs used for biomedical imaging are composed of a heavy metal core such as cadmium selenide (CdSe), cadmium telluride (CdTe), or indium phosphide (InP), surrounded by a stabilizing shell like zinc sulfide (ZnS) or zinc selenide (ZnSe). This core–shell architecture enhances photostability and reduces toxic metal ion leakage [5,6]. For example, QD800 nanoparticles composed of a CdSe/CdTe core with a ZnS shell have been successfully conjugated to EGFR antibodies for in vivo imaging of SCC margins [8]. To improve safety, cadmium-free alternatives like ZnCuInSe/ZnS have emerged, offering comparable brightness and longer circulation times with reduced cytotoxicity [10]. Surface functionalization further tailors QDs for biomedical use. Common coatings include polyethylene glycol (PEG), sulfobetaine polymers, and amphiphilic lipids, which increase water solubility, reduce aggregation, and enable ligand attachment [7,14]. The net surface charge, especially positive zeta potentials, can influence non-specific cellular uptake, as demonstrated in 3D models of HNSCC spheroids [11].

2.2. Photostability and Fluorescence Quantum Yield

A defining feature of QDs is their superior photostability. Unlike

traditional organic dyes that rapidly photobleach, QDs can emit strong fluorescence signals for extended imaging periods, even under prolonged excitation. This property enables continuous intraoperative visualization without signal loss [6,15]. Quantum yield, the efficiency of photon emission following excitation, can exceed 50% for many core–shell QDs, making them among the brightest fluorophores available for biomedical use [5,16]. This brightness is preserved even in tissue-dense environments, facilitating deeper signal penetration when operating in the near-infrared (NIR) range (~700–800 nm). For instance, QD800 and ZnCuInSe/ZnS QDs exhibit high signal-to-noise ratios when applied to SCC tumor models, enhancing visualization of tumor–stroma interfaces [9,10].

2.3. Multiplexing Capacity for Multi-Marker Imaging

QDs can be engineered to emit distinct colors based on their core size and composition, allowing simultaneous detection of multiple tumor biomarkers in a single imaging session (Table 1). This multiplexing capability is especially advantageous in tumors with heterogeneous cellular populations or complex microenvironments. For example, Hu et al. utilized a panel of QDs (QD565–705) to map EGFR, E-cadherin, and vimentin expression in SCC tissues, achieving predictive accuracy for lymph node metastasis with area-under-the-curve (AUC) values >0.90 [4]. The broad excitation spectrum and narrow emission peaks of QDs also support spectrally resolved imaging systems, enabling precise spatial localization of multiple targets without signal overlap. When paired with computational deconvolution and time-gated imaging, QDs can outperform traditional dyes in both clarity and diagnostic value [5,7].

QD Type	Core/Shell	Emission Peak	Targeting Ligand	Imaging Modality	Unique Features
QD800 (CdSe/CdTe-ZnS)	Near-infrared QD	800 nm	EGFR, RGD	In vivo optical fluorescence	High tumor-to-background ratio
CdSe/ZnS (PEG-coated)	Visible red QD	625 nm	None (MSC carrier)	Ex vivo fluorescence imaging	MSC delivery; low toxicity, tumor-homing
ZnCuInSe/ZnS	Cadmium-free NIR QD	750 nm	A20 peptide	Time-gated microscopy	Deep tissue imaging, antifouling polymer shell
CdSe/CdS/ZnS	Visible/NIR QD	610 nm	A20 peptide	Confocal imaging	Uptake driven by zeta potential
QD565–705 (varied)	Multiplex panel	565–705 nm	EGFR, vimentin	Immunohistofluorescence (IHF)	Multiplex margin labeling in FFPE tissue

Table 1: Summary of Quantum Dot Design Features and Imaging Characteristics

3. Targeting Strategies for Skin Cancer Margins

NMSCs, including BCC and SCC, often overexpress specific surface biomarkers such as epidermal growth factor receptor (EGFR), integrins (e.g., $\alpha\beta3$, $\alpha\beta6$), nucleolin, and folate

receptor- α , which provide a foundation for molecularly targeted imaging strategies [5,17,18]. Among these, EGFR is particularly relevant in SCC and has been effectively targeted using monoclonal antibody–conjugated QDs for real-time intraoperative imaging of

tumor margins [4,8]. Bioconjugation techniques play a critical role in enabling specific tumor targeting. QDs can be functionalized with peptides (e.g., iRGD, RGD, A20FMDV2), antibodies (e.g., anti-EGFR, anti-HER2), or aptamers (e.g., AS1411 against nucleolin), facilitating either receptor-mediated endocytosis or high-affinity binding to tumor-associated antigens [7,11,16] (Table 2). In a notable example, $\alpha\beta3$ -integrin-targeting QDs conjugated to RGD peptides demonstrated selective tumor accumulation in head and neck squamous cell carcinoma, offering a clear analog for cutaneous SCC targeting. Similarly, EGFR-targeted QDs successfully delineated tumor boundaries in vivo within minutes of administration [8,9]. These approaches reflect the broader dichotomy between passive and active targeting. Passive targeting relies on the enhanced permeability and retention (EPR) effect that allows nanoscale agents like QDs to accumulate within tumor tissue due to leaky vasculature and poor lymphatic drainage [7]. However, passive accumulation alone may be insufficient for high-resolution margin detection. Active targeting, achieved

through ligand-mediated recognition of tumor biomarkers, offers superior specificity and is more effective for distinguishing tumor periphery during surgical resection [12,17]. Emerging delivery platforms such as skin-derived mesenchymal stem cells (MSCs) have also shown promise. These cells naturally home to tumor sites and can transport QDs into the tumor microenvironment without compromising viability or migration, demonstrating a novel delivery method with potential applications in margin visualization [12]. Additionally, multifunctional QDs designed for simultaneous imaging and therapy (theranostics) have been explored in epithelial tumors, further highlighting the translational potential of these systems for NMSC [5,16]. Together, these strategies suggest that bioconjugated QDs, whether peptide-, antibody-, or aptamer-linked, offer a robust and tunable platform for precise visualization of tumor margins (Table 3). This is especially important for superficial tumors like NMSC, where maximizing tissue conservation without compromising oncologic control remains paramount.

Biomarker	Relevance to NMSC	Targeting Ligand Used
EGFR	Overexpressed in SCC	Monoclonal antibody
$\alpha\beta3$ integrin	Neovasculature in SCC	RGD peptide
$\alpha\beta6$ integrin	Overexpressed in SCC	A20FMDV2 peptide
E-cadherin	Tumor suppression loss	Anti-E-cadherin mAb
Vimentin	EMT marker	Anti-vimentin mAb
Folate receptor	Expressed in SCC/BCC	Folic acid, aptamer

Table 2: Biomarkers and Targeting Strategies for Quantum Dot Conjugation in NMSC

Study	QD Type	Emission (nm)	Targeting Ligand	Tumor Model	Application	Key Findings
Yang et al., 2011	CdSe/CdTe-ZnS (QD800)	800	Anti-EGFR mAb	Buccal SCC (mouse)	In vivo fluorescence imaging	Specific margin labeling, 15 min onset, signal peaks at 1h, declines by 8h
Huang et al., 2013	CdSe/ZnS (QD800)	800	cRGDfC ($\alpha\beta3$ integrin)	HNSCC angiogenic vessels	In vivo angiogenesis visualization	Targeted vasculature, high TBR, NIR imaging through skin
Hu et al., 2016	QD565–705	565–705	EGFR, E-cadherin, vimentin	HNSCC FFPE specimens	Multiplexed biomarker mapping	Predictive of LNM; QD-IHF superior to IHC; AUC > 0.90
Yakovets et al., 2020	ZnCuInSe/ZnS	750	A20 peptide ($\alpha\beta6$ integrin)	FaDu HNSCC spheroids	3D tumor imaging	High SNR, time-gated imaging; selective labeling in tumor spheroids

Dirheimer et al., 2024	CdSe/CdS/ZnS	610	A20 peptide (non-specific)	HSC-3 tongue SCC spheroids	3D margin labeling	Uptake driven by positive zeta potential, not specific binding
Dapkute et al., 2017	CdSe/ZnS	625	None (MSC delivery)	Breast cancer (MDA-MB-231, mouse)	Stem cell-mediated delivery	Tumor-homing MSCs deliver QDs with high specificity; minimal off-target signal

Table 3: Quantum Dot Platforms for Margin Visualization in Epithelial Tumors

4. Quantum Dot Imaging Platforms

QD-based imaging systems are emerging as transformative tools in dermatologic oncology, offering both in vivo and ex vivo platforms for enhanced tumor margin visualization. Their unmatched brightness, photostability, and multiplexing capabilities allow for dynamic imaging strategies tailored to the specific needs of skin cancer surgery. In vivo visualization leverages the fluorescence of surface-functionalized QDs administered systemically or locally to delineate tumor margins in real-time. Near-infrared QDs, such as QD800, enable deep tissue imaging with reduced background autofluorescence and have been successfully used to target integrins and EGFR in squamous cell carcinoma [8,9]. This facilitates fluorescence-guided surgery, where surgeons can visualize tumor borders intraoperatively using QD-labeled molecular markers. In murine models, EGFR-targeted QDs have demonstrated clear signal accumulation at cutaneous tumor edges within 15 minutes of injection, with optimal signal-to-noise ratios sustained up to 6 hours [8]. Ex vivo visualization platforms are equally valuable for margin assessment immediately after tissue excision. Liu et al. (2019) showed that fluorescent probes applied topically to excised NMSC specimens provided spatial resolution within 100 μm of histologically confirmed tumor margins [3]. Time-gated imaging systems, such as the LI-COR Odyssey scanner, further enhance QD signal clarity by suppressing autofluorescence and enabling spectral deconvolution, particularly when imaging cadmium-based or indium phosphide QDs. The integration of QDs with dermatoscopic and microscopic tools represents a promising frontier. QD-assisted fluorescence dermatoscopy could improve early diagnostic sensitivity for subclinical BCC and SCC, especially when using multiplexed QDs tuned to specific tumor and stromal biomarkers. Additionally, coupling QDs with reflectance confocal microscopy (RCM) or multiphoton fluorescence imaging allows high-resolution, depth-resolved imaging of tumor architecture, which is particularly relevant for margin control in ambiguous or infiltrative lesions. Confocal-compatible QD systems have been tested in spheroid models to visualize marker expression in live tissue analogs, and time-gated detection methods enhance visualization of QD-labeled tumor borders even in thick tissue slices [7,10]. Overall, quantum dot imaging platforms enable

scalable and modular systems that can be adapted for real-time surgical navigation, rapid ex vivo pathology, and integrated preoperative mapping, all with the goal of maximizing precision and minimizing recurrence in NMSC resection.

5. Preclinical and Emerging Clinical Evidence

QDs have demonstrated strong promise in preclinical settings for delineating tumor margins in NMSC, particularly SCC and BCC (Table 4). Animal model studies, excised human specimen imaging, and comparative analyses with other fluorophores such as indocyanine green (ICG) provide converging evidence of QDs' utility in surgical guidance. In vivo animal models have shown robust tumor labeling using QDs conjugated to EGFR antibodies or integrin-targeting peptides. In an SCC xenograft model, QD800-labeled anti-EGFR probes enabled real-time tumor margin visualization within 15 minutes post-injection [8]. Similarly, studies utilizing integrin-targeted QDs demonstrated specific accumulation in $\alpha\text{v}\beta\text{3}$ - and $\alpha\text{v}\beta\text{6}$ -overexpressing tumors, with significant signal enhancement and margin clarity [9,10]. Ex vivo imaging studies further support the role of QDs in surgical margin delineation. Applying a near-infrared cathepsin-activatable probe to excised SCC and BCC specimens, achieved spatial concordance with histopathologic margins within 100 μm [3]. While QDs were not used directly in the tissue samples, QD-loaded phantoms demonstrated sharper edge response and higher signal fidelity than traditional fluorescent agents, underscoring their potential in rapid intraoperative use. Comparative evaluations with standard fluorophores such as ICG reveal the advantages of QDs. ICG suffers from low photostability, rapid clearance, and broad tissue distribution, limiting its effectiveness for margin precision. QDs, in contrast, offer brighter emission, reduced photobleaching, and multiplex imaging capability [4,18]. Furthermore, time-gated detection enabled by QDs minimizes background autofluorescence and enhances tumor-to-margin contrast [10]. Collectively, these findings indicate that QDs outperform conventional contrast agents in specificity, durability, and multi-marker visualization. As cadmium-free QD formulations advance, clinical translation for real-time margin assessment during Mohs or wide local excision procedures appears increasingly feasible.

Delivery Method	Carrier System	Benefits
Stem Cell-mediated	Human skin-derived MSCs	Tumor tropism, minimal off-target
Direct IV injection	QD + EGFR/RGD peptide	Rapid tumor localization
Topical + ex vivo scan	Cathepsin-activated dye (control study)	High margin resolution (~100 μm)
Intratumoral injection	QD-liposomes	Controlled release, reduced toxicity
Microneedle-assisted	Gold or polymer QD analogs	Enhanced dermal penetration

Table 4: Delivery Strategies for Quantum Dots in Skin Cancer Models

6. Safety and Regulatory Considerations

Despite their promise, the clinical translation of QDs for surgical margin visualization is hindered by concerns over toxicity, biocompatibility, and regulatory approval. The heavy metal content of traditional cadmium-based QDs, such as CdSe/ZnS core-shell structures, has raised significant concerns regarding long-term tissue accumulation, oxidative stress, and potential carcinogenicity [5,6]. Studies have reported that cadmium ions released through degradation or oxidation can induce reactive oxygen species (ROS) production and mitochondrial damage, particularly in hepatic and renal systems [18]. To address these challenges, biodegradable and cadmium-free QDs are being actively developed. Carbon quantum dots (CQDs), graphene quantum dots (GQDs), and silicon-based QDs offer comparable photostability and fluorescence performance while reducing systemic toxicity [13,15]. For instance, CQDs derived from organic sources have demonstrated effective tumor labeling and minimal off-target effects in vivo, while GQDs have served as photosensitizers in photodynamic therapy with high efficacy and biocompatibility [6]. Additionally, ternary alloy QDs such as CuInSe/ZnS have been explored for their near-infrared emission and lower environmental risk [10]. Regulatory challenges remain a significant barrier to intraoperative adoption. While platforms like Cornell Dots (silica-based QDs) have progressed to clinical trials for melanoma imaging, no QD system has received full regulatory approval for surgical margin visualization in skin cancer [13]. Hurdles include stringent safety evaluations, unclear long-term biodistribution profiles, and limited standardization across imaging systems. Surface modifications such as PEGylation, zwitterionic coatings, and antibody conjugation have helped reduce immunogenicity, yet regulatory agencies continue to emphasize the need for robust pharmacokinetic, toxicity, and clearance data prior to approval [5,16].

Going forward, clinical translation will likely depend on: Transition to non-toxic, biodegradable QD systems; Integration with existing FDA-approved surgical platforms; and Evidence from large-scale animal and early-phase human studies confirming safety and accuracy. These developments are critical to ensure that QDs can move from promising preclinical tools to practical, regulatory-compliant agents for intraoperative use in dermatologic oncology.

7. Discussion

The next frontier in QD research for NMSC margin visualization lies in smart, multiplexed platforms that not only illuminate tumors

but dynamically guide clinical decision-making. Innovations in QD design, targeting strategies, and computational integration are shaping a translational roadmap toward personalized fluorescence-guided surgery (FGS). Multiplexed QD systems, capable of emitting at distinct wavelengths, offer the ability to simultaneously label tumor cells, stromal elements, immune infiltrates, and neovasculature within a single surgical field [4,5]. For example, QDs conjugated to EGFR, $\alpha\text{v}\beta\text{6}$ integrin, and E-cadherin have been used to delineate cancerous epithelium, tumor-stroma interfaces, and epithelial-to-mesenchymal transition zones, providing a comprehensive tumor map in real-time [10,18]. Emerging “smart” QDs are engineered to respond to biochemical stimuli in the tumor microenvironment, such as pH changes, enzymatic activity (e.g., cathepsin cleavage), or oxidative stress, to enhance contrast only in malignant zones [3]. These context-sensitive probes could allow adaptive margin visualization, where fluorescence intensity or emission spectrum shifts based on tissue pathology, helping surgeons distinguish between inflamed, dysplastic, and malignant tissue. Integration with artificial intelligence (AI) further extends the potential of QDs beyond simple imaging. Machine learning algorithms trained on spectral and spatial data can assist in intraoperative classification of tissue types, margin adequacy prediction, and even alerting surgeons of high-risk zones in real time [13]. AI-enhanced platforms could also calibrate QD signal thresholds, minimize false-positives from autofluorescence, and enable precision resection with minimal healthy tissue loss.

Clinical translation of these tools will depend on:

- Development of cadmium-free, FDA-compliant QDs with standardized emission profiles
- Real-world validation in Mohs surgery and excisional procedures
- Incorporation into AI-augmented imaging systems and portable dermatoscopic devices

In this evolving paradigm, QDs are poised not merely as fluorescent tags, but as intelligent surgical co-pilots, navigating the invisible boundaries between normal and neoplastic skin. QDs represent a transformative innovation in the visualization of surgical margins for non-melanoma skin cancers. Their unique optical properties, including high photostability, narrow emission spectra, and tunable fluorescence, make them ideal for real-time, high-resolution imaging in cutaneous oncology. Whether used in vivo during fluorescence-guided surgery or ex vivo on resected specimens, QDs offer unparalleled precision in defining tumor

boundaries, potentially reducing recurrence rates and improving patient outcomes. Despite these advantages, several barriers hinder their routine clinical adoption. Concerns about heavy metal toxicity, limited regulatory frameworks, and challenges in achieving targeted delivery without off-tissue accumulation remain unresolved. Nonetheless, the development of biodegradable QDs, improved bioconjugation strategies, and integration with artificial

intelligence are actively addressing these limitations. Looking ahead, QD platforms are poised to move beyond static imaging and into the realm of intelligent, multiplexed, and adaptive systems that inform surgical decisions in real time (Table 5). With continued interdisciplinary research and regulatory support, quantum dots hold significant translational promise for enhancing the precision and safety of skin cancer surgery.

Platform	Clinical Application	Translation Stage	Challenges Remaining
Cornell Dots (C-dots)	Melanoma imaging (SLN)	Human trials	Scale-up, targeting flexibility
QD800-EGFR	SCC margin delineation	Preclinical	Immunogenicity, cadmium content
QD800-RGD	Angiogenesis visualization	Preclinical	Need for biodegradable QDs
ZnCuInSe/ZnS QDs	HNSCC 3D imaging	Preclinical	Delivery in live tumors
NAC-CdTe/CdS QDs	DNA biosensing (in vitro)	Early-stage	Tissue-specific targeting needed

Table 5: Clinical and Translational Potential of QDs in NMSC

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