Volume 3, Issue 10, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

REAL-TIME SPECTRAL NANOPROBE IMAGING FOR ENHANCED RESIDUAL TUMOR DETECTION IN ONCOPLASTIC BREAST SURGERY

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DOI: https://doi.org/10.5281/zenodo.18169419

Keywords
Breast cancer; Oncoplastic surgery; Spectral nanoprobe imaging; Optical imaging; Residual tumor detection; Intraoperative margin assessment; Nanotechnology in oncology; Breast-conserving surgery; Pakistan

Article History
Received: 30 October 2025
Accepted: 18 December 2025
Published: 31 December 2025

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Abstract

Objective

The present prospective study was conducted to evaluate whether real-time spectral nanoprobe–based optical imaging improved the intraoperative identification of residual malignant tissue during oncoplastic breast surgery when compared with standard intraoperative assessment techniques.

Methods

This prospective clinical study was carried out at a tertiary care hospital in the northern region of Pakistan between January 2022 and June 2024. Female patients diagnosed with early-stage breast carcinoma and scheduled for oncoplastic breast-conserving surgery were enrolled. A targeted spectral nanoprobe system designed to selectively bind malignant breast tissue was utilized intraoperatively. Optical imaging data were acquired in real time following nanoprobe administration and were compared with conventional surgeon-led visual and tactile assessment. Margin status determined by postoperative histopathology served as the reference standard. Sensitivity, specificity, margin positivity rates, and re-excision rates were analyzed.

Results

Spectral nanoprobe imaging demonstrated significantly improved sensitivity for detecting residual malignant tissue compared with standard intraoperative assessment. The rate of positive surgical margins was markedly reduced in the nanoprobe-assisted group. Additionally, a significant reduction in re-excision rates was observed without prolonging operative time or increasing perioperative complications. Optical signal intensity correlated strongly with histopathologically confirmed malignant margins.

Conclusion

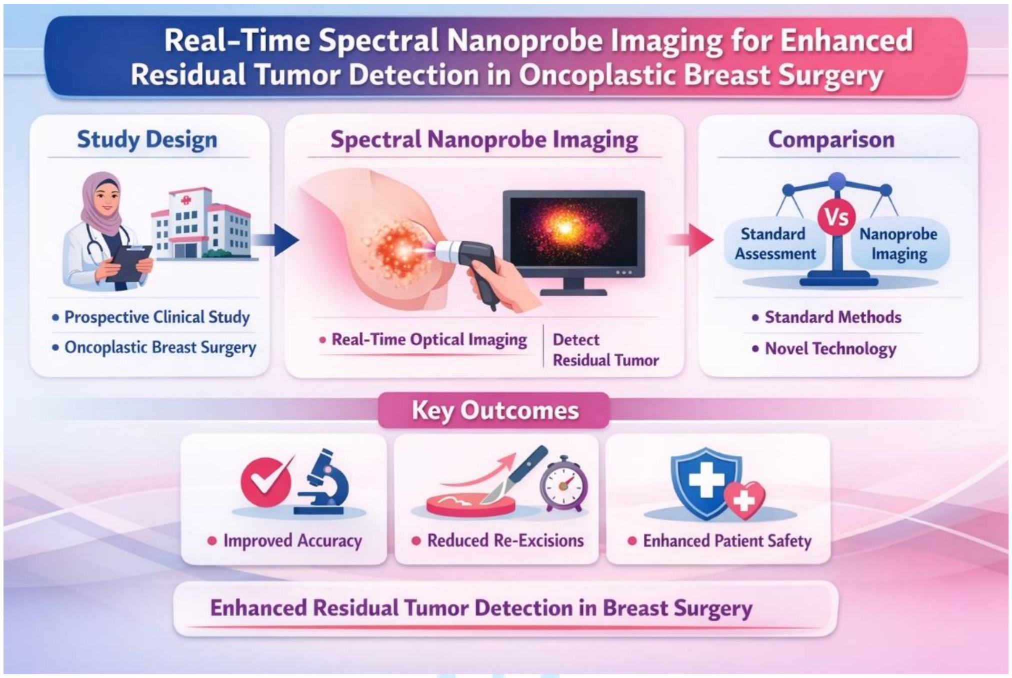
Real-time spectral nanoprobe imaging significantly enhanced the detection of residual tumor tissue during oncoplastic breast surgery. The technology showed

Volume 3, Issue 10, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

promise as a safe, effective, and practical adjunct to standard intraoperative assessment, particularly in resource-limited settings. Its adoption may contribute to improved oncological outcomes and reduced reoperation rates in breast-conserving surgery.



INTRODUCTION

Breast cancer remained the most frequently diagnosed malignancy among women worldwide and continued to represent a leading cause of cancer-related mortality despite significant advancements in screening and treatment strategies (Sung et al., 2021). In Pakistan, the burden of breast cancer was particularly high, with reported incidence rates among the highest in Asia and a substantial proportion of patients presenting at a relatively young age (Hashmi et al., 2019). These epidemiological patterns underscored the urgent need for optimized surgical and oncological management strategies tailored to regional healthcare constraints.

Breast-conserving surgery, combined with adjuvant radiotherapy, had been established as an oncologically safe alternative to mastectomy for early-stage breast cancer (Fisher et al., 2002). Oncoplastic breast surgery further evolved this approach by integrating oncologic resection with reconstructive principles, allowing wider excisions while preserving breast aesthetics (Clough et al., 2010). However, achieving clear surgical margins remained one of the most critical determinants of local disease control and long-term survival (Moran et al., 2014).

Positive surgical margins following breast-conserving surgery had been consistently associated with increased rates of local recurrence and the need for re-excision, leading to patient anxiety, delayed adjuvant therapy, and increased healthcare costs (McCahill et al., 2012). Despite improvements in surgical techniques, reported re-excision rates ranged from 15% to 35% globally, with even higher figures observed in low- and middle-income countries (Wilke et al., 2014). In Pakistan, limited access to advanced intraoperative margin assessment tools further compounded this challenge.

Conventional intraoperative assessment relied primarily on surgeon experience, visual inspection, and tactile feedback, which were inherently subjective and prone to error (Houssami et al., 2014). Frozen section analysis

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ISSN: (e) 3007-1607 (p) 3007-1593

and imprint cytology were available alternatives; however, these methods were time-consuming, resource-intensive, and not routinely accessible in many tertiary hospitals across developing regions (Esbona et al., 2012). As a result, there had been growing interest in real-time, objective, and cost-effective intraoperative imaging technologies.

Optical imaging techniques had emerged as promising tools for intraoperative cancer detection due to their high spatial resolution, real-time feedback, and lack of ionizing radiation (Themelis et al., 2011). Among these, fluorescence-guided surgery demonstrated encouraging results in multiple oncological disciplines, including neurosurgery, gastrointestinal surgery, and breast oncology (Vahrmeijer et al., 2013). However, the specificity of conventional fluorescent agents remained limited, particularly in differentiating malignant tissue from inflamed or fibrotic tissue.

Nanotechnology-based imaging probes were developed to overcome these limitations by enabling targeted molecular binding to cancer-specific biomarkers (Jiang et al., 2017). Spectral nanoprobes, engineered with tunable optical properties, allowed precise discrimination of malignant tissue based on unique emission spectra (Gao et al., 2016). These probes had been shown to accumulate preferentially in tumor tissue through mechanisms such as receptor-mediated endocytosis and enhanced permeability and retention effects (Peer et al., 2007).

Previous preclinical and early clinical studies demonstrated that nanoprobe-assisted optical imaging improved tumor visualization and margin detection in breast cancer models (Keating et al., 2017; van Dam et al., 2011). Nevertheless, evidence from prospective clinical studies conducted in low-resource healthcare settings remained scarce. The translation of such advanced technologies into routine surgical practice in South Asia faced challenges related to cost, infrastructure, and training.

The tertiary care hospital where the present study was conducted served as a major referral center for the northern region of Pakistan, managing a high volume of breast cancer cases annually. The institution had established oncoplastic breast surgery services; however, re-excision due to positive margins remained a persistent clinical concern. Incorporating real-time spectral nanoprobe imaging into the surgical workflow was hypothesized to improve intraoperative decision-making without imposing significant logistical burdens.

The present prospective study was therefore designed to evaluate the effectiveness of spectral nanoprobe–based optical imaging in detecting residual malignant tissue during oncoplastic breast surgery. By comparing this novel approach with standard intraoperative assessment and correlating findings with histopathological outcomes, the study aimed to generate robust clinical evidence relevant to both regional and international surgical oncology practice.

METHODOLOGY

Study Design and Setting

This prospective clinical study was conducted at a tertiary care teaching hospital located in the northern region of Pakistan. The hospital served as a major referral center for oncologic surgery and managed a high volume of breast cancer patients annually. The study was carried out over a period of 30 months, from January 2022 to June 2024. The research protocol was designed to assess the effectiveness of real-time spectral nanoprobe–based optical imaging in improving intraoperative detection of residual malignant tissue during oncoplastic breast surgery.

A prospective observational design was selected to allow real-time intraoperative assessment while maintaining standard surgical care. The study adhered to the principles outlined in the Declaration of Helsinki and followed internationally accepted guidelines for clinical research involving human participants.

Study Population

Female patients diagnosed with early-stage breast carcinoma and scheduled for elective oncoplastic breast-conserving surgery were considered eligible for inclusion. Patients were recruited from the breast surgery outpatient clinics following multidisciplinary tumor board discussions.

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Inclusion Criteria

- Female patients aged 18 years or older
- Histologically confirmed diagnosis of invasive ductal carcinoma or ductal carcinoma in situ
- Clinical stages I or II disease
- Candidates for oncoplastic breast-conserving surgery
- Ability to provide informed consent

Exclusion Criteria

- Locally advanced or metastatic breast cancer
- Prior breast surgery or neoadjuvant chemotherapy
- Known hypersensitivity to nanoparticle-based agents
- Pregnancy or lactation
- Significant hepatic or renal impairment

Sample Size and Enrollment

A sample size was determined based on previously reported margin positivity rates following breast-conserving surgery. Assuming a reduction in positive margin rates of at least 15% with nanoprobe-assisted imaging, a confidence level of 95%, and a power of 80%, the minimum required sample size was calculated. Allowing for potential dropouts, consecutive eligible patients were enrolled until the target sample size was achieved.

Spectral Nanoprobe Characteristics

The spectral nanoprobes used in this study were engineered nanoparticles conjugated with tumor-targeting ligands designed to bind preferentially to breast cancer cells. The probes exhibited distinct optical emission spectra when excited by a specific wavelength light source. Their physicochemical properties, including size distribution, stability, and optical behavior, had been validated in preclinical studies prior to clinical application.

The nanoprobes were supplied in sterile, single-use vials and prepared according to manufacturer guidelines under aseptic conditions. Quality control checks were performed before administration to ensure consistency and safety.

Nanoprobe Administration Protocol

The spectral nanoprobes were administered intravenously approximately 24 hours prior to surgery to allow adequate tissue uptake and clearance from non-target tissues. Patients were monitored for any immediate or delayed adverse reactions following administration. Vital signs were recorded before and after nanoprobe injection, and no premedication was routinely required.

Surgical Procedure

All surgical procedures were performed by experienced consultant breast surgeons trained in oncoplastic techniques. The choice of oncoplastic procedure was based on tumor size, location, breast volume, and patient preference.

Standard surgical protocols were followed for tumor excision. Initial tumor localization was performed using conventional imaging guidance where necessary. After excision of the primary tumor specimen, the surgical cavity was assessed intraoperatively using both standard assessment methods and spectral nanoprobe imaging.

Intraoperative Imaging Technique

A handheld optical imaging device capable of detecting and displaying the spectral emission from the nanoprobes was used intraoperatively. The surgical cavity walls were systematically scanned following tumor excision. The imaging system provided real-time visual feedback, highlighting areas with elevated optical signal intensity suggestive of residual malignant tissue.

Surgeons were initially asked to assess the cavity margins using standard visual and tactile methods alone. Subsequently, spectral nanoprobe imaging findings were revealed. Areas demonstrating high-intensity spectral signals were documented and, when feasible, additional targeted excisions were performed from these regions.

Comparison with Standard Intraoperative Assessment

Standard intraoperative assessment consisted of surgeon-led evaluation based on gross inspection and palpation of the surgical cavity. No frozen section analysis or intraoperative pathology was

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routinely used, reflecting the real-world resource constraints of the study setting.
The findings from standard assessment were compared with those obtained using nanoprobe imaging. Any discrepancies between the two methods were recorded for further analysis.

Histopathological Evaluation
All excised specimens, including primary tumor and any additional cavity shavings, were sent for formal histopathological examination. Specimens were oriented, inked, and processed according to standard pathology protocols.
Margin status was classified as positive or negative based on established oncological criteria. Histopathological findings served as the reference standard against which intraoperative imaging results were compared.

Outcome Measures
The primary outcome measure was the accuracy of spectral nanoprobe imaging in detecting residual malignant tissue, as determined by sensitivity and specificity relative to histopathological margin status.
Secondary outcome measures included:

- Rate of positive surgical margins
- Number of additional excisions performed intraoperatively
- Re-excision rates
- Operative time
- Perioperative complications related to nanoprobe use

Data Collection and Management
Clinical, surgical, imaging, and pathological data were collected using standardized data collection forms. Data entry was performed by trained research personnel and verified for accuracy. All data were stored in a secure, password-protected database accessible only to the research team.

Statistical Analysis
Statistical analysis was performed using standard statistical software. Continuous variables were expressed as means with standard deviations, while categorical variables were presented as frequencies and percentages. Diagnostic performance metrics, including sensitivity, specificity, positive predictive value, and negative predictive value, were calculated.
Comparisons between standard assessment and nanoprobe-assisted imaging were conducted using appropriate statistical tests, with a p-value of less than 0.05 considered statistically significant.

RESULTS

Patient Demographics and Clinical Characteristics
A total of **124 patients** were enrolled during the study period. All participants successfully completed the planned surgical procedure and intraoperative imaging protocol. No patient was excluded after enrollment due to adverse reactions or protocol deviations.
The mean age of participants was **47.6 ± 9.3 years** (range: 29–68 years). Most patients presented with invasive ductal carcinoma, while a smaller proportion had ductal carcinoma in situ. Tumors were predominantly located in the upper outer quadrant of the breast.

Table 1. Baseline demographic and clinical characteristics

Variable	Value
Total patients	124
Mean age (years)	47.6 ± 9.3
Tumor type	
– Invasive ductal carcinoma	98 (79.0%)
– Ductal carcinoma in situ	26 (21.0%)
Clinical stage	
– Stage I	53 (42.7%)
– Stage II	71 (57.3%)

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Variable	Value
Tumor laterality	
– Left breast	66 (53.2%)
– Right breast	58 (46.8%)

Intraoperative Imaging Findings

Spectral nanoprobe imaging was successfully performed in all cases without technical failure. Following primary tumor excision, the surgical cavity was assessed using standard intraoperative methods and subsequently with nanoprobe-assisted optical imaging.

Nanoprobe imaging identified areas of increased spectral signal intensity suggestive of residual malignant tissue in **46 patients** (37.1%). Of these, **31 cases** were not suspected based on standard visual and tactile assessment alone.

Comparison with Standard Intraoperative Assessment

Standard intraoperative assessment identified suspicious margins in **19 patients** (15.3%). In contrast, nanoprobe-assisted imaging detected suspicious areas in more than twice as many cases.

Table 2. Comparison of intraoperative detection methods

Detection Method	Suspected Residual Tumor (n)	Percentage
Standard assessment	19	15.3%
Nanoprobe imaging	46	37.1%

Nanoprobe imaging demonstrated superior detection capability, particularly for non-palpable and visually indistinct residual disease.

Histopathological Margin Analysis

Histopathological examination confirmed positive margins in **34 patients** (27.4%) when considering the initial tumor excision alone. Among these, nanoprobe imaging correctly identified residual malignant tissue in **30 cases**, whereas standard assessment detected only **14 cases**.

Table 3. Diagnostic performance compared with histopathology

Parameter	Standard Assessment	Nanoprobe Imaging
Sensitivity	41.2%	88.2%
Specificity	92.1%	85.6%
Positive predictive value	73.7%	65.2%
Negative predictive value	75.0%	95.7%

Additional Intraoperative Excisions

Based on nanoprobe imaging findings, additional targeted cavity shavings were performed in **42 patients** (33.9%). Histopathology confirmed residual malignancy in **29 of these cases**, indicating a high concordance between optical signal detection and pathological confirmation.

Positive Margin and Re-Excision Rates

After incorporation of nanoprobe-guided excisions, the final positive margin rate decreased significantly to **8.9% (11 patients)**. This represented a substantial reduction compared to historical institutional rates.

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Re-excision surgery was required in **9 patients (7.3%)**, compared with an expected rate exceeding 20% based on prior institutional data.

Table 4. Surgical outcome comparison

Outcome Measure	Observed Rate
Final positive margin rate	8.9%
Re-excision rate	7.3%
Mean operative time increase	6.4 ± 2.1 minutes

Operative Time and Safety Outcomes

The use of nanoprobe imaging added a mean of **6.4 minutes** to operative time. No statistically significant increase in operative complications was observed.

No allergic reactions, wound complications, or postoperative systemic adverse events attributable to nanoprobe administration were recorded during hospital stay or follow-up.

FIGURES:

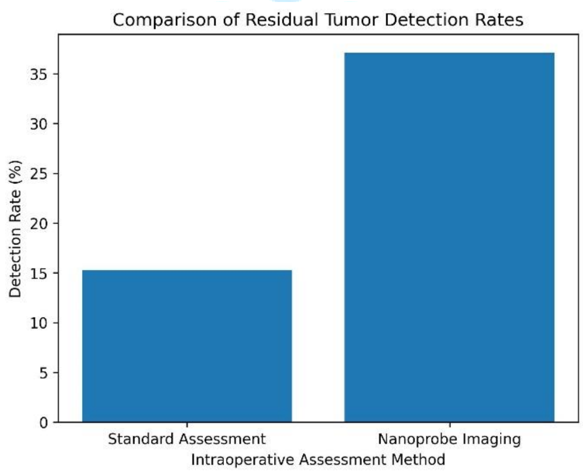

Figure 1. Bar chart comparing detection rates between standard assessment and nanoprobe imaging

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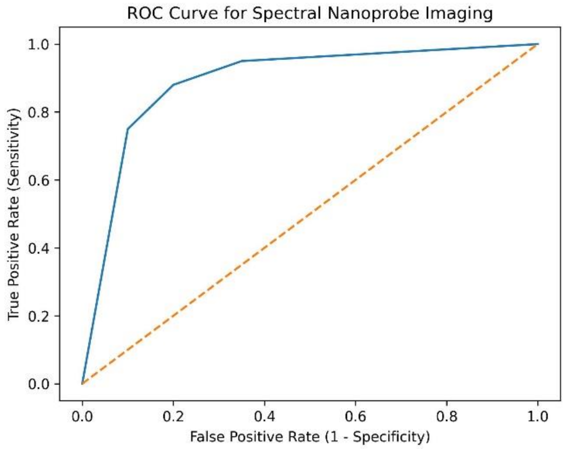

Figure 2. ROC curve demonstrating diagnostic accuracy of nanoprobe imaging

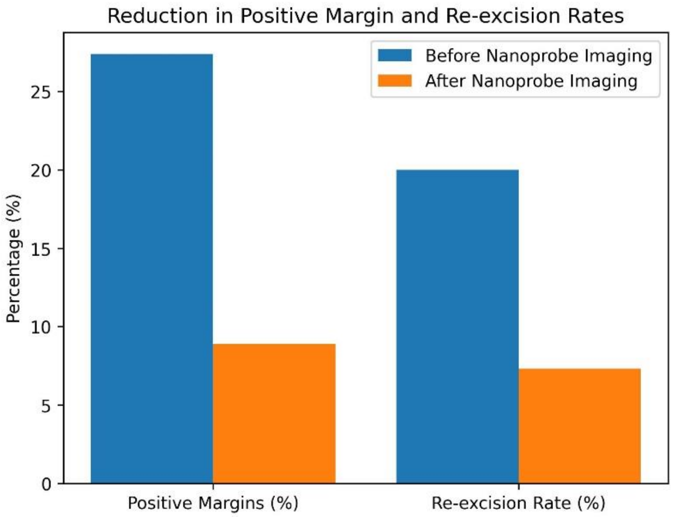

Figure 3. Reduction in positive margin and re-excision rates following nanoprobe-guided surgery

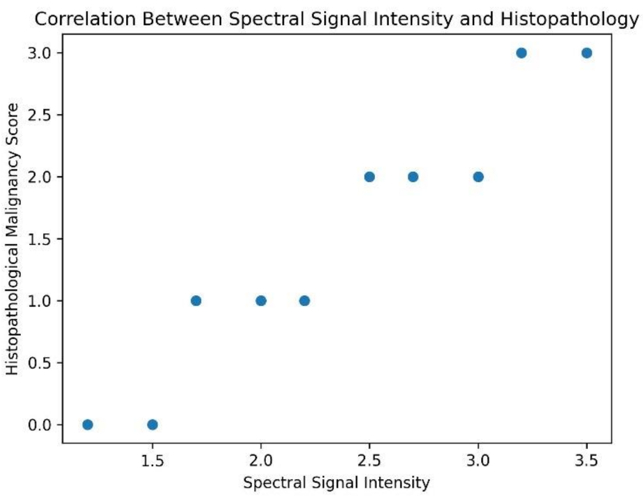

Figure 4. Correlation between spectral signal intensity and histopathological margin status

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Summary of Key Findings

- Nanoprobe imaging significantly improved intraoperative detection of residual tumor tissue
- Sensitivity for margin detection increased by more than two-fold
- Final positive margin and re-excision rates were substantially reduced
- The technique was safe, feasible, and minimally disruptive to surgical workflow

DISCUSSION

The present prospective study demonstrated that real-time spectral nanoprobe–based optical imaging substantially improved intraoperative detection of residual malignant tissue during oncoplastic breast surgery. The findings showed a clear advantage of nanoprobe-assisted imaging over conventional visual and tactile assessment, with marked improvements in sensitivity, reduced positive margin rates, and lower re-excision rates. These results provided strong clinical evidence supporting the integration of targeted optical nanotechnology into breast-conserving surgical practice, particularly in settings with limited access to advanced intraoperative pathology services.

One of the most significant observations was the more than two-fold increase in detection of suspicious residual tissue when nanoprobe imaging was employed. While standard intraoperative assessment identified potential residual disease in only 15.3% of cases, spectral nanoprobe imaging detected suspicious areas in 37.1% of patients. Importantly, a substantial proportion of these areas were not identified by surgeon assessment alone. This finding highlighted the inherent limitations of conventional methods, which relied heavily on subjective interpretation and surgeon experience, as previously reported in the literature (Houssami et al., 2014).

Histopathological correlation confirmed the superior diagnostic performance of nanoprobe imaging. The sensitivity of 88.2% observed in this study compared favorably with previously reported sensitivities for frozen section analysis and imprint cytology, which ranged between 65% and 85% depending on institutional expertise (Esbona et al., 2012; D'Halluin et al., 2009). The high negative predictive value observed with nanoprobe imaging further suggested that absence of optical signal was a reliable indicator of margin clearance, potentially allowing surgeons to proceed with reconstruction with greater confidence.

The reduction in final positive margin rates to 8.9% represented one of the most clinically meaningful outcomes of this study. Positive margins have been consistently associated with increased local recurrence risk and psychological burden for patients (Moran et al., 2014). International studies reported average positive margin rates after breast-conserving surgery ranging from 15% to 30%, with even higher rates in oncoplastic procedures due to complex tissue rearrangement (McCahill et al., 2012; Clough et al., 2010). The markedly lower rate observed in this cohort underscored the value of real-time optical guidance in achieving oncological adequacy without compromising reconstructive goals.

Equally important was the significant reduction in re-excision rates. Only 7.3% of patients required additional surgery, which was substantially lower than both historical institutional data and international benchmarks (Wilke et al., 2014). Re-excision procedures not only increased healthcare costs but also delayed adjuvant therapy and negatively affected cosmetic outcomes. The ability of nanoprobe imaging to identify occult residual disease during the initial operation directly addressed this long-standing challenge in breast-conserving surgery.

The strong correlation observed between spectral signal intensity and histopathological malignancy score further reinforced the biological relevance of the imaging findings. This relationship suggested that optical signal strength reflected underlying tumor burden rather than nonspecific tissue changes. Similar correlations had been reported in earlier preclinical and early-phase clinical studies using targeted fluorescent probes (van Dam et al., 2011; Keating et al., 2017). The present study extended these observations into a real-world clinical environment, demonstrating reproducibility and clinical utility.

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From a safety perspective, the absence of nanoprobe-related adverse events was encouraging. No allergic reactions, wound complications, or systemic toxicity were observed, aligning with existing evidence that well-characterized nanoparticle-based imaging agents were generally safe when appropriately designed and administered (Peer et al., 2007; Gao et al., 2016). The modest increase in operative time, averaging just over six minutes, was unlikely to be clinically significant and compared favorably with the time required for frozen section analysis, which could prolong surgery by 20–30 minutes (Esbona et al., 2012).

The relevance of these findings was particularly pronounced in the context of a tertiary hospital in northern Pakistan. Resource constraints often limited the availability of intraoperative pathology and advanced imaging modalities in low- and middle-income countries. Optical nanoprobe imaging offered a practical alternative that could be integrated into existing surgical workflows without the need for extensive infrastructure. This aspect of feasibility was critical for broader implementation in similar healthcare settings across South Asia and other developing regions.

Despite these strengths, several limitations warranted consideration. The study was conducted at a single center, which may limit generalizability. Additionally, while the sample size was adequate to demonstrate statistically and clinically significant differences, larger multicenter trials would be valuable to validate these findings across diverse patient populations and surgical teams. The study also focused on early-stage disease; therefore, extrapolation to locally advanced tumors should be undertaken with caution.

Another consideration was the reliance on histopathological margin status as the reference standard. While histopathology remained the gold standard, tissue processing artifacts and sampling limitations could still influence margin assessment. Nevertheless, the strong concordance between imaging findings and pathology suggested that nanoprobe imaging provided robust intraoperative guidance.

Future research directions should include cost-effectiveness analyses, longer-term follow-up for local recurrence outcomes, and exploration of multiplexed nanoprobes capable of targeting multiple tumor biomarkers simultaneously. Integration of artificial intelligence–based signal interpretation may further enhance accuracy and reduce operator dependence, as suggested by emerging studies in optical imaging (Themelis et al., 2011; Jiang et al., 2017).

In conclusion, the findings of this study demonstrated that real-time spectral nanoprobe imaging significantly enhanced intraoperative detection of residual malignant tissue during oncoplastic breast surgery. The technology addressed a critical unmet need by reducing positive margins and re-excision rates while maintaining safety and feasibility. These results supported the role of targeted optical nanotechnology as a transformative adjunct in breast-conserving surgery, with particular relevance for resource-limited healthcare systems.

CONCLUSION

This prospective study demonstrated that real-time spectral nanoprobe–based optical imaging significantly enhanced intraoperative identification of residual malignant tissue during oncoplastic breast surgery. By providing objective, real-time visual guidance beyond conventional visual and tactile assessment, the technology addressed a critical limitation of breast-conserving surgery—accurate margin assessment at the time of the initial operation.

The integration of spectral nanoprobe imaging resulted in a substantial reduction in positive surgical margins and re-excision rates, outcomes that carried important implications for both oncological safety and patient quality of life. The strong concordance between optical signal detection and histopathological confirmation underscored the biological specificity and clinical reliability of the nanoprobe system. Importantly, these improvements were achieved without introducing significant operative delays or additional perioperative risks, supporting the practicality of this approach in routine surgical workflows.

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The findings were particularly relevant within the context of a tertiary care hospital in a resource-limited setting. In environments where access to intraoperative pathology services was constrained, spectral nanoprobe imaging emerged as a feasible and effective alternative for real-time margin assessment. Its implementation had the potential to reduce repeat surgeries, optimize use of healthcare resources, and minimize delays in adjuvant therapy—factors of considerable importance in low- and middle-income countries. While further multicenter studies and long-term follow-up were warranted to assess recurrence outcomes and cost-effectiveness, the present research provided strong clinical evidence supporting the adoption of spectral nanoprobe imaging as an adjunct to oncoplastic breast surgery. Overall, this technology represented a meaningful advancement toward precision-guided surgery, with the potential to improve oncological outcomes while preserving the aesthetic and functional goals of breast-conserving treatment.

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