Original Article

Cutting-edge insights: near-infrared imaging for surgical margin assessment in head and neck tumor resection: a systematic review and meta-analysis

Ke Li[#], Jiajin Yang[#], Haosen Lian, Zixi Tian, Chunjie Li, Ning Gao, Zhiyong Guo^

State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Head and Neck Oncology, West China Hospital of Stomatology, Sichuan University, Chengdu, China

Contributions: (I) Conception and design: K Li, Z Guo, C Li, N Gao; (II) Administrative support: C Li, N Gao; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: K Li, J Yang, H Lian, Z Tian; (V) Data analysis and interpretation: K Li, J Yang, H Lian, Z Tian, Z Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Zhiyong Guo, MD, PhD; Ning Gao, MD. State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Head and Neck Oncology, West China Hospital of Stomatology, Sichuan University, No. 14 Section Three Renmin Nan Road, Chengdu 610041, China. Email: zhiyongguo@scu.edu.cn; gaoningdaniell@163.com.

Background: In head and neck cancer (HNC), real-time evaluation of tumor margin status following surgical excision of the tumor is of critical importance. This systematic review aimed to assess the effectiveness of near-infrared fluorescence (NIRF) imaging for the real-time delineation of tumor margins in HNC resections.

Methods: Two investigators independently conducted a comprehensive search following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines across the PubMed, Scopus, Embase, and China National Knowledge Infrastructure (CNKI) databases until August 1st, 2023. Observational studies were included, while other studies with inappropriate study design were excluded. The primary outcomes included the specificity, sensitivity, and area under the summary receiver operating characteristic (SROC) curve when using NIRF imaging to assess surgical margins. We compared fluorescence in the resection specimen margins and residual fluorescence in the surgical cavity margins as methods of utilizing NIRF to evaluate surgical margins. Diagnostic trial quality was assessed, and statistical heterogeneity was determined.

Results: The initial search yielded 1,607 articles. After reviewing the full texts, seven articles with 103 patients were included, among which five were incorporated for quantitative analysis. The selected studies had an average score of 10.1 of quality. Heterogeneity analysis revealed I^2 values of 26% [95% confidence interval (CI): 0–100%] and 78% (95% CI: 52–100%) for NIRF specimen imaging with close margin considered positive or negative. Comparing NIRF imaging to the gold standard of pathology for surgical margin diagnosis, with close margin considered positive, sensitivity and specificity in excised specimens were 0.84 (95% CI: 0.39–0.98) and 0.96 (95% CI: 0.80–0.99), respectively. When a close margin was considered negative, sensitivity and specificity were 0.98 (95% CI: 0.10–1.00) and 0.96 (95% CI: 0.45–1.00), respectively. The areas under the SROC curves were 0.97 (95% CI: 0.95–0.98) and 0.99 (95% CI: 0.98–1.00), respectively. A quantitative analysis of residual fluorescence at surgical cavity margins was not performed due to an insufficient number of studies.

^ ORCID: 0000-0001-8791-0020.

Conclusions: NIRF imaging is a promising method for real-time surgical margin assessment of HNC. With its robust diagnostic capabilities in excised tumor specimens, it is also an effective technique for detecting residual tumor fluorescence in the surgical cavity for supplementary assessment. But the results should be interpreted with caution.

Keywords: Surgical margin assessment; real-time imaging; near-infrared fluorescence imaging (NIRF imaging); head and neck cancer (HNC); meta-analysis

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Introduction

Surgical excision is the primary treatment modality for head and neck cancers (HNC). The primary objective of surgical intervention in the management of HNC is the complete eradication of the neoplastic lesion while simultaneously preserving the integrity of the adjacent healthy tissue within this intricate anatomical and functional domain. Ultimately, a pathologically confirmed negative margin status is inextricably linked to a reduced risk of local recurrence, improved progression-free interval, and enhanced overall survival, establishing it as the most pivotal predictive factor for HNC (1,2). This is particularly noteworthy when residual disease is identified at or in close proximity to the surgical margins, and the incidence of localized recurrence substantially escalates (3,4). Failure to achieve pristine surgical margins may necessitate supplementary therapeutic modalities, including chemotherapy, radiotherapy, and/or further surgical intervention (5). Given the intricate nature and critical role of structures in the head and neck region, along with the imperative need for optimal functional and aesthetic outcomes, the standards for margin status in HNC resection remain rigorously stringent.

Nevertheless, the positivity rate of surgical margins in the treatment of HNC remains considerably high. In national and institutional cohort studies, 11% to 26% of HNC patients exhibit positive surgical margins after resection (6,7). Conventionally, the assessment of resection margins has relied predominantly on subjective visual, tactile, and experiential evaluations conducted by surgeons. Nevertheless, these assessments, reliant upon subjective discernment of subtle variations in tissue density and surface morphology, are not sufficient for the detection of residual disease.

Presently, the established standard of care for detecting residual tumors involves sampling the primary specimen and its margins, followed by frozen section analysis. However, this technique has some limitations. The first constraint lies in the inherent subjectivity and potential for error in sampling tumor margins, resulting in a high probability of false negative assessments. The second constraint manifests as a requirement for the tumor specimen to exit the surgical suite after resection. In doing so, the specimen often loses its orientation relative to the surgical bed, and frozen section analysis incurs exorbitant costs and is a time-intensive process (8).

Near-infrared fluorescence (NIRF) imaging has recently emerged as a prospective method for real-time tumor visualization and localization during HNC surgery. Compared to existing intraoperative guidance methods, such as radioactive seed localization, its significance lies in its capability to offer non-invasive, real-time, high-resolution images of biological structures and processes, thereby minimizing radiation exposure (9,10). The real-time imaging capabilities of this technology allow for the superimposition of fluorescent images atop conventional bright-field imagery, significantly simplifying the correlation between signals and anatomical structures. Although there are many preoperative imaging methods for tumors, such as computed tomography (CT) and positron emission tomography-CT (PET-CT), there is currently no approved real-time method for intraoperative tumor imaging. However, NIRF imaging can aid physicians in swiftly evaluating surgical outcomes, enabling immediate adjustments. NIRF not only improves surgical outcomes but also minimizes time costs by considering changes in tumor positions through real-time tracking, thereby enhancing post-operative comfort for patients (11,12). Compared to other methods used for tumor margin imaging, such as narrow-band imaging, NIRF imaging is more precise in delineating the tumor border (13). Employing near-infrared

(NIR) light with wavelengths of approximately 650–900 nm to excite tumor-targeted fluorescent probes enhances intraoperative margin delineation and detection of residual tumors. These fluorescent probes enable the visualization of tumor margins and the surgical cavity, consequently increasing the rate of successful resection. This technology has utility both intraoperatively and *ex vivo*, as tracers can selectively bind to tumor tissues, a binding that persists even after tumor excision. Moreover, *ex vivo* imaging allows the meticulous control of imaging parameters (14,15).

However, despite the existence of a systematic review on this subject, a meta-analysis has not yet been conducted, and there may be instances of underreporting (16). We conducted a systematic review of the literature adhering to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) reporting checklist (17,18) (available at https://qims.amegroups.com/article/view/10.21037/qims-24-564/rc), aiming to analyze the efficacy and diagnostic role of NIRF imaging methods in margin assessment after HNC resection.

Methods

Search strategy

The search methodology, study selection, and reporting in this study were conducted in accordance with the PRISMA-DTA guidelines, using the Participants, Interventions, Comparisons, Outcomes, and Study Design (PICOS) criteria for systematic reviews as follows:

- ❖ Population: patients undergoing interventions for HNC.
- ❖ Intervention: surgical resection guided by NIRF.
- ❖ Comparator: histopathological analysis of tissues, which is the gold standard for diagnosis.
- ❖ Outcomes: sensitivity, specificity, and area under the curve.
- ❖ Studies: prospective and retrospective studies.

PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (http://www.embase.com), China National Knowledge Infrastructure (CNKI; https://www.cnki.net), and Scopus (https://www.scopus.com) databases were searched from inception until August 1st, 2023 for studies involving NIRF-guided HNC resection. Peer-reviewed clinical articles were searched using terms such as “fluorescence-guided surgery”, “head and neck tumors”, and their synonyms. Each search query for a specific database was optimized (Appendix 1).

Eligibility criteria

The systematic review, adhering to PRISMA-DTA guidelines and PICOS criteria, included studies utilizing NIRF imaging technology to assess surgical resection margins in HNC.

Studies meeting at least one of the following criteria were excluded from this systematic review: (I) inappropriate study design for this review (case series/reports, experimental or laboratory studies, literature reviews, letters to editors, personal opinions of authors, books/chapters, and conference abstracts); (II) repetitive studies and/ or studies with results unrelated to the topic; (III) studies not yet peer-reviewed or formally accepted; and (IV) studies on other imaging modalities (narrowband imaging, high-resolution microscopic endoscopy imaging, and others) without involving NIRF. This study aimed to evaluate the effectiveness of NIRF imaging in diagnosing the post-operative margins of HNC resections.

Study selection

Studies were selected in two distinct phases. In the initial phase, two independent reviewers (K.L. and J.Y.) meticulously evaluated the eligibility of all titles and abstracts retrieved from the search databases, excluding articles that did not meet the predetermined criteria. Subsequently, in the second phase, the remaining articles were independently scrutinized by the same two reviewers to identify the articles contributing to this systematic review. A third author (H.L.) critically assessed this process and resolved potential discrepancies through consensus discussions. Additionally, manual searches were conducted for references to the selected articles and prominent scientific journals pertinent to the field of oral and maxillofacial surgery.

Data items and collection

The data collection process included gathering the following information: author names, publication year, affiliated hospital or medical institution, research objectives, number of included patients, tumor type, tumor staging information, tumor location, diagnostic criteria for the target disease, fluorophore type, administration of fluorophores, imaging protocols, outcomes, general demographic characteristics of the study population, and study conclusions. One reviewer (K.L.) extracted the general study features and results, which were independently verified by another reviewer

(J.Y.). Any discrepancies were resolved through consensus discussions with additional reviewers (H.L. and Z.T.).

Study quality assessment

Two researchers (K.L. and J.Y.) independently analyzed methodological quality. The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used. This tool includes four domains: patient selection, index test, reference standard, and flow and timing. Each domain was evaluated for bias risk, and the first three domains for applicability, leading to a clearer assessment of bias and applicability in primary studies on diagnostic accuracy. Each domain was categorized as low, high, or unclear risk (19).

For this analysis, methodological quality assessment was performed using Review Manager version 5.4.

Statistical analysis

We employed random- and mixed-effects models for the standard diagnostic test accuracy (DTA) meta-analysis (20,21). Sensitivity and specificity were summarized, and summary receiver operating characteristic (SROC) curves were constructed to estimate the diagnostic accuracy (according to the area under the curve). Statistical heterogeneity was determined using the I-square (I^2) statistic: ≤25% indicated low heterogeneity (acceptable), >25% and ≤50% indicated moderate heterogeneity (moderate), >50% and ≤75% indicated high heterogeneity (substantial), and >75% indicated very high heterogeneity (significant) (22). The possible threshold effect was assessed using Spearman's correlation coefficient. Statistical analysis was performed using Stata software (Statistics and Data 18th edition, RRID: SCR_012763) for the meta-analysis, with a confidence interval (CI) of 95%. A P value of ≤0.05 was considered statistically significant.

Studies lacking the complete data to construct a 2×2 table were excluded from the meta-analysis of diagnostic test features, although they may have been included in the overall synthesis of results in the systematic review to facilitate analysis.

Results

Search results and characteristics

A total of 1,607 articles were retrieved from the four databases. After removing duplicates (n=395), 1,212 articles were screened for titles and abstracts, of which 998 were excluded. The primary reasons for exclusion were topics unrelated to the research objectives and an inappropriate study design. After a full-text review of the remaining 214 studies, 207 were excluded. The reasons for exclusion included unrelated results (n=88), inappropriate study design (n=73), other imaging modalities (n=37), and repetitive studies (n=9). For articles with overlapping populations, we comprehensively evaluated the quality of experimental design, sample size, and publication date to select one article from the same clinical trial for inclusion (Appendix 2). Finally, seven articles were included in the systematic review (*Figure 1*) (23-29).

The studies included in this systematic review were published between 2017 and 2023. Among them, 5 were prospective studies (23-25,28,29) and 2 were retrospective studies (26,27). Additionally, 5 studies were single-arm studies (24,26-29), while 2 were cohort studies (23,25). The primary outcomes measured in these studies were the sensitivity, specificity, and area under the curve for detecting HNC surgical margins. These studies included 103 patients who underwent surgery to assess the diagnostic accuracy of surgical margins using NIRF. The margin status was assessed by evaluating the edges of excised specimens (25,28) in two studies, through the surgical cavity in one study (29), and by both approaches simultaneously in four studies (23,24,26,27). The reference standard for all seven included studies was pathological examination. Disease characteristics and imaging protocols were reported in the seven included studies, encompassing a total of 103 HNC patients, with the majority having squamous cell carcinoma (94 cases, 91%). Overall, among the studies providing tumor staging information, there were a total of 30 T1–2 tumors (51%) and 29 T3–4 tumors (49%). Four articles employed nonspecific fluorophores, three of which utilized free monomeric indocyanine green (ICG) (24,26,29), while the other investigated ONM-100 (OncoNano Medicine-100) (27), a pH-sensitive amphiphilic polymer that can assemble into micelles with ICG chelated in the micelle core. As for the specific targeted fluorescent agents used, one study employed panitumumab-IRDye800CW (28), and two studies used cetuximab-IRDye800CW (23,25). One study administered the fluorescent agent over 30 min before surgery (26), whereas the remaining six studies administered it 24 hours or more prior to surgery (23-25,27-29). These findings' data are summarized in *Table 1*.

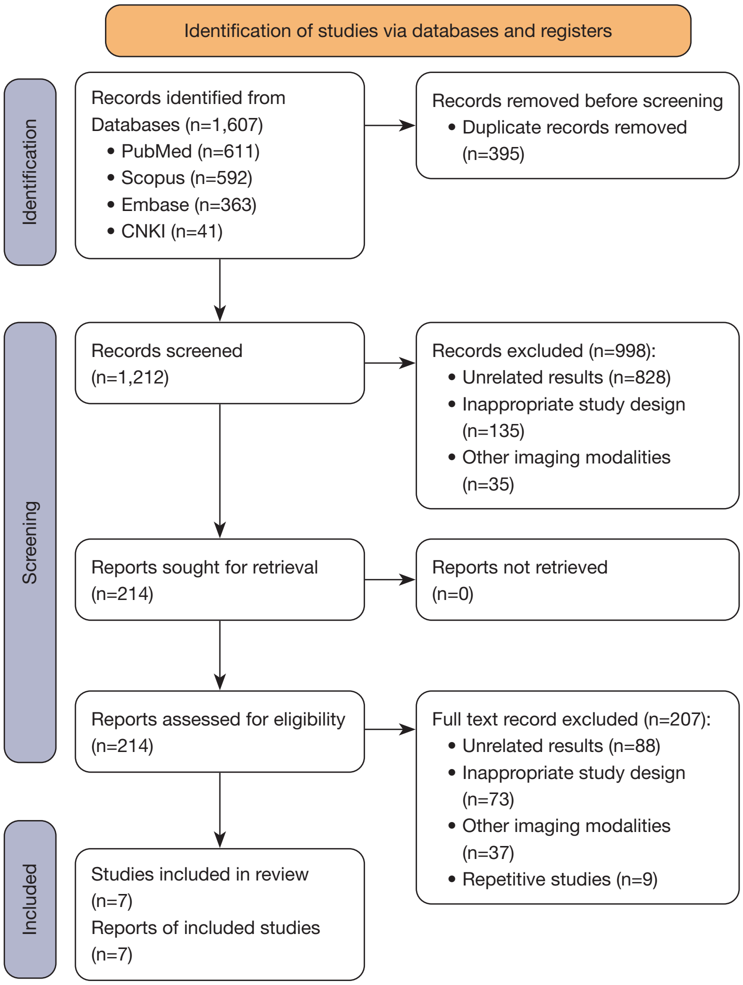

Figure 1 Identification of studies from databases and registers. CNKI, China National Knowledge Infrastructure.

Risk of bias and quality assessment

The quality of the selected studies was assessed using a customized QUADAS-2 tool. When using QUADAS-2, we evaluated the risk of bias for the four domains: patient selection, index test, reference standard, and flow and timing. Additionally, we assessed applicability for the three domains: patient selection, index test, and reference standard. It is worth noting that the "flow and timing" domain of QUADAS-2 does not involve an applicability assessment. Instead, this domain primarily focuses on evaluating the internal validity concerning the timing and sequence of the diagnostic process within the studies (19,30). The total score for each study was calculated by adding the number of criteria met, with a higher score indicating a higher quality of evidence (*Figure 2*). Overall, the number of implemented quality assurance measures implemented in each study ranged from 8 to 12 (out of a total of 13). Across the four QUADAS-2 tool domains mentioned earlier, each study had an average of 10.1 quality assurance measures. The study by Richard *et al.* presents two "unclear" aspects in terms of risk of bias and one "unclear" and one "high risk" aspect in applicability (29). Notably, Stubbs *et al.*'s study had a "high risk" aspect in terms of risk of bias (24).

Heterogeneity analysis showed I^2 values of 26% (95% CI: 0–100%) and 78% (95% CI: 52–100%) for NIRF specimen imaging with positive or negative close margins.

The diagnostic accuracy of NIRF imaging in tumor specimens

When collecting textual data, we observed that certain articles pertaining to the classification of tumor margin

Table 1 Systematized table with patient characteristics and qualitative data from included studies

Study	Study country	Temporal perspective	Study design	Tumor type	Tumor stage		Fluorophores	Fluorophore administration	Imaging protocols	No. of patients	Age (years), mean ± SD
					T1–T2	T3–T4					
Moore *et al.* (23), 2017	The Netherlands	Prospective	Cohort study	HNSCC 15	NA	NA	Cetuximab-IRDye800CW	Infused intravenously before surgery 3–7 d	Preoperative imaging, surgical cavity imaging, specimen imaging	15	NA
Stubbs *et al.* (24), 2019	USA	Prospective	Single-arm study	PACC 1, PSCC 2, OSCC 11	NA	NA	ICG	Injected preoperatively 24 h	Preoperative imaging, surgical cavity imaging, specimen imaging	14	58.9±12.3
Voskuil *et al.* (25), 2020	The Netherlands	Prospective	Cohort study	HNSCC 15	NA	NA	Cetuximab-IRDye800CW	Injected intravenously 4 d prior to surgery	Preoperative imaging, surgical cavity imaging, specimen imaging	15	62.2
Pan *et al.* (26), 2020	China	Retrospective	Single-arm study	OSCC 20	12	8	ICG	Infused intravenously over 30 min before imaging	Preoperative imaging, surgical cavity imaging, specimen imaging	20	60±9
Steinkamp *et al.* (27), 2021	The Netherlands	Retrospective	Single-arm study	HNSCC 13	7	6	ONM-100	Infused intravenously before surgery 24±8 h	Surgical cavity imaging, specimen imaging	13	66.77±13.62
Krishnan *et al.* (28), 2022	USA	Prospective	Single-arm study	OSCC 18	6	12	Panitumumab-IRDye800CW	Infused intravenously before surgery 1–5 d	Specimen imaging	18	NA
Richard *et al.* (29), 2023	USA	Prospective	Single-arm study	PTC 5, SACC 1, OMMT 2	5	3	ICG	Infused intravenously 24 h before the surgery	Preoperative imaging, specimen imaging	8	15.95±6.93

SD, standard deviation; HNSCC, head and neck squamous cell carcinoma; NA, not applicable; USA, the United States of America; PACC, parotid adenoid cystic carcinoma; PSCC, parotid squamous cell carcinoma; OSCC, oral squamous cell carcinoma; PTC, papillary thyroid carcinoma; SACC, salivary adenoid cystic carcinoma; OMMT, otolaryngologic malignancy of the musculoskeletal tumor; ICG, indocyanine green; ONM-100, OncoNano Medicine-100; h, hours; d, days.

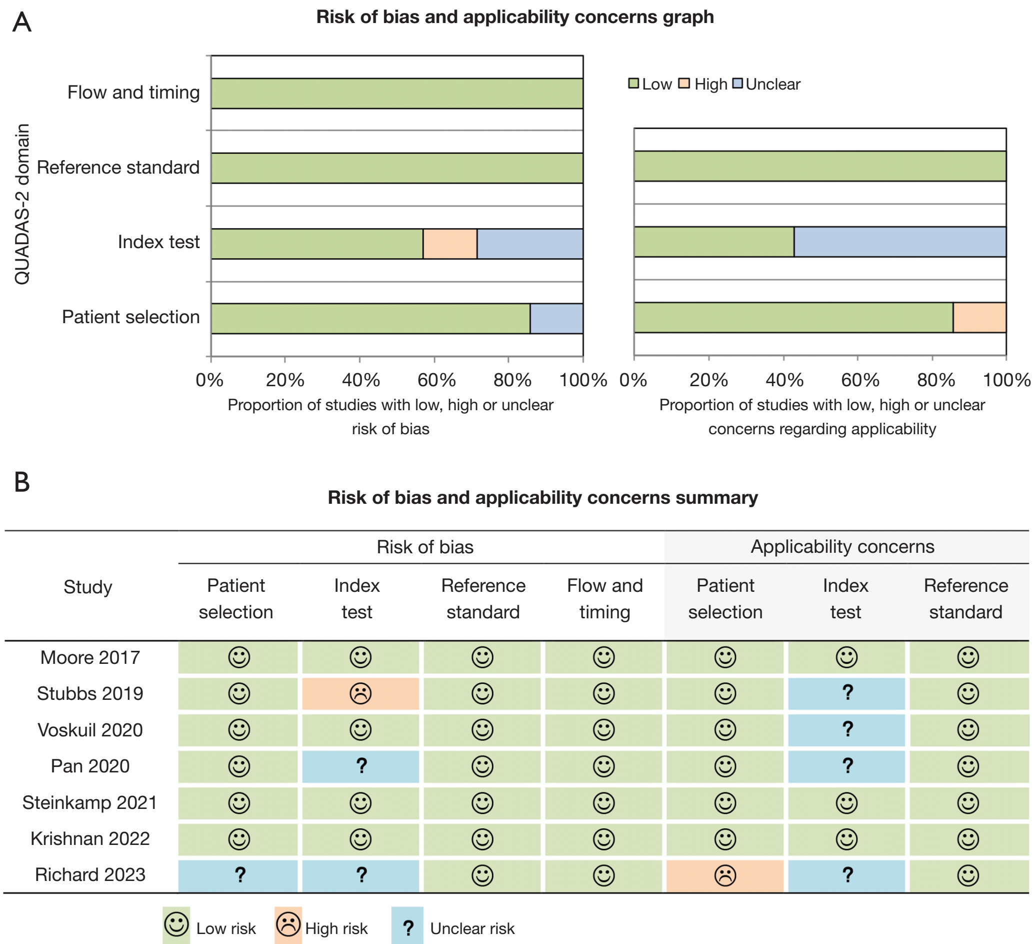

Figure 2 Display of risk of bias and applicability concerns. (A) Risk of bias and applicability concerns graph presents the assessment results of the study's risk of bias. (B) Risk of bias and applicability concerns summary presents the specific content of the risk of bias and applicability concerns associated with the studies, included in the review.

status deviated from the binary categorization. Instead, they adopted a trinary classification encompassing the category close. However, during distinct stages of tumor excision, it is imperative to apply divergent surgical margin criteria (31,32). Consequently, we incorporated the 'close' margin into either positive or negative margins, facilitating separate analyses and discussions. Our study included different sites and types of HNC with a relatively small sample size. The original studies used varying guidelines to define margins; therefore, we adopted fluorescence standards from the original studies.

We analyzed the diagnostic accuracy of NIRF imaging in determining the surgical margin status. Five studies with 80 participants included close margins as positive margins and used NIRF imaging to determine the margin status of the tumor specimens. The pooled results reported a sensitivity of 0.84 (95% CI: 0.39–0.98; *Figure 3*), specificity of 0.96 (95% CI: 0.80–0.99; *Figure 3*), and an area under SROC curve of 0.97 (95% CI: 0.95–0.98; *Figure 4*). Four studies involving 66 participants included a close margin as a negative margin, and their pooled results reported a sensitivity of 0.98 (95% CI: 0.10–1.00; *Figure 5*), specificity of 0.96 (95% CI: 0.45–1.00; *Figure 5*), and an area under the SROC curve of 0.99 (95% CI: 0.98–1.00; *Figure 6*).

No statistically significant differences were observed when threshold effects were explored. The Spearman correlation coefficients were Spearman's rho =−0.3441, P=0.5563, and Spearman's rho =−0.5443 and P=0.6310 for the two classifications of including close margins as positive margins and including close margins as negative margins,

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krishnan 2022	15	0	0	3	1.00 (0.78–1.00)	1.00 (0.29–1.00)
Steinkamp 2021	9	1	2	1	0.82 (0.48–0.98)	0.50 (0.01–0.99)
Voskuil 2020	4	1	0	10	1.00 (0.40–1.00)	0.91 (0.59–1.00)
Pan 2020	2	0	2	16	0.50 (0.07–0.93)	1.00 (0.79–1.00)
Stubbs 2019	0	0	1	13	0.00 (0.00–0.97)	1.00 (0.75–1.00)
Combined					0.84 (0.39–0.98)	0.96 (0.80–0.99)
Heterogeneity: I^2 =26%, 95% CI = [0–100%]						

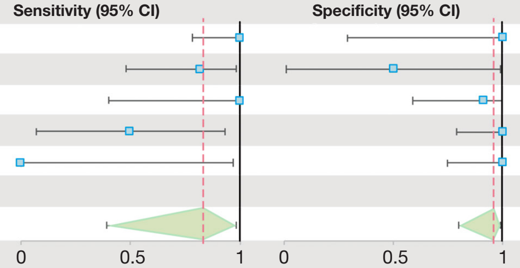

Figure 3 Accuracy of individual studies on NIRF imaging of HNC specimens for surgical margin status. The close margin is included in positive margins. TP, true positive; FP, false positive; FN, false negative; TN, true negative; CI, confidence interval; NIRF, near-infrared fluorescence; HNC, head and neck cancer.

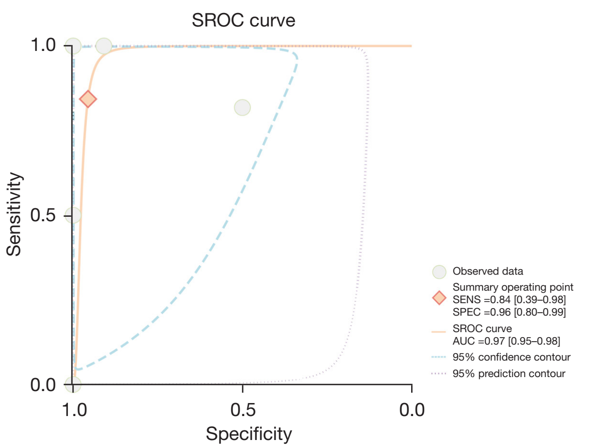

Figure 4 SROC curve of NIRF imaging of HNC specimens for surgical margin status. The close margin is included as a positive margin. SROC, summary receiver operating characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve; NIRF, near-infrared fluorescence; HNC, head and neck cancer.

respectively.

The diagnostic accuracy of NIRF imaging in the surgical cavity

Five studies evaluated the utility of NIRF in assessing residual cancer in the surgical cavity/tumor bed post-resection (23,24,26,27,29). However, owing to the limited data available, a meta-analysis was not feasible.

In four studies with clearly recorded results, sensitivity ranged from 33.33% to 100%, and specificity ranged from 85.71% to 100% in detecting residual cancer cells in the tumor bed post-resection. In a study by Pan *et al.*, 4/20 patients showed ICG fluorescence abnormalities in the tumor bed, and two of them had confirmed positive surgical margins (26). Richard *et al.* and Steinkamp *et al.* also successfully utilized this method to determine the surgical margin status in 6/8 and 9/13 patients, respectively (27,29). In a study by Stubbs *et al.*, all 14 patients showed no fluorescent residue in the surgical cavity, and pathological examination confirmed the accuracy of the surgical margin assessment (24).

Strength of NIRF

Four of the seven articles mentioned recorded NIRF intensity using the mean fluorescence intensity (MFI) or tumor-to-background ratio (TBR). TBR assesses the clarity of the target signal relative to background noise, while MFI represents the average fluorescence intensity of all detected particles or cells in the sample. Using both TBR and MFI together provides a comprehensive understanding of the fluorescence signal's intensity and clarity. However, due to variations in imaging systems, types of fluorophores, and limited data, we did not perform a pooled data analysis (33). Two studies used non-specific fluorophores. In a study by Pan *et al.*, *ex vivo* specimens were bisected, and the mean fluorescence intensities of tumor tissues, peritumoral tissues, and normal tissues were 380.15±141.24, 268.52±79.12, and 262.12±90.16 arbitrary units, respectively; the signal-to-background ratios (SBR) for tumor versus peritumoral and normal tissues were 1.38±0.22 and 1.43±0.27, respectively (26). In a study by Steinkamp *et al.*, surgical cavity-driven margin assessment identified four fluorescent lesions, with three cases of positive or close margins having a mean TBR of 4.68 (range, 2.2–6.2). Using specimen-driven margin assessment, the median TBR for positive deep resection margins was 3.36±1.62 (27). Two studies

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krishnan 2022	5	0	0	13	1.00 (0.48–1.00)	1.00 (0.75–1.00)
Steinkamp 2021	6	4	0	3	1.00 (0.54–1.00)	0.43 (0.10–0.82)
Voskuil 2020	4	1	0	10	1.00 (0.40–1.00)	0.91 (0.59–1.00)
Pan 2020	2	0	2	16	0.50 (0.07–0.93)	1.00 (0.79–1.00)
Combined					0.98 (0.10–1.00)	0.96 (0.45–1.00)

Heterogeneity: I^2 =78%, 95% CI = [52%–100%]

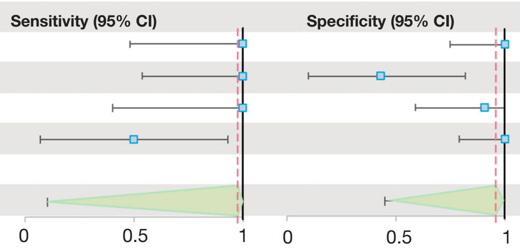

Figure 5 Accuracy of individual studies on NIRF imaging of HNC specimens for surgical margin status. The close margin is included as a negative margin. TP, true positive; FP, false positive; FN, false negative; TN, true negative; CI, confidence interval; NIRF, near-infrared fluorescence; HNC, head and neck cancer.

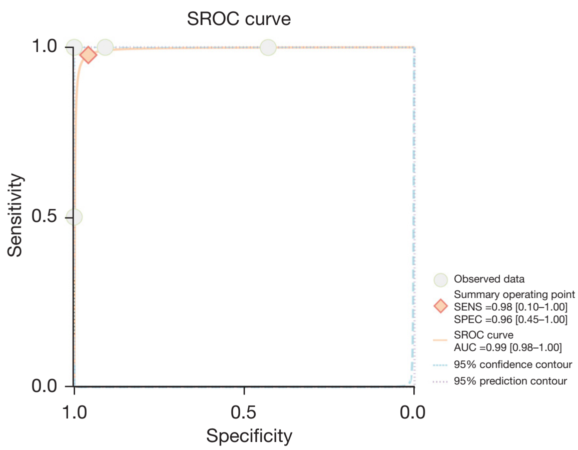

Figure 6 SROC curve of NIRF imaging of HNC specimens for surgical margin status. The close margin is included as a negative margin. SROC, summary receiver operating characteristic; SENS, sensitivity; SPEC, specificity; AUC, area under the curve; NIRF, near-infrared fluorescence; HNC, head and neck cancer.

used the specific fluorophore cetuximab-IRDye800CW. In Voskuil *et al.*'s study, the TBR ranged from 1.61±0.93 to 3.10±2.53 across different cohorts, with an increase in TBR in the pre-dosing cohort (25). In Moore *et al.*'s study, all patients, except for the microdose group, had a peak TBR greater than 2 (range, 2.2–14.1) for primary *in situ* tumor imaging. The pre-resection fluorescence intensity of the primary *in situ* tumor (20.6±4.6) was significantly greater than the background fluorescence (6.3±0.5) and the post-resection wound bed fluorescence (2.0±0.8) (23).

Discussion

Ensuring appropriate surgical margins is a crucial aspect of HNC surgical treatment, as it can preserve the integrity of the surrounding structures while increasing the extent of tumor removal (34). This systematic review aimed to summarize the effectiveness of NIRF guidance in HNC surgery. This meta-analysis focused on demonstrating the diagnostic capability of NIRF in determining the status of surgical margins.

Principal findings

We approached Richard *et al.*'s study with caution as it included children and adolescents. However, the study by Richard *et al.* only involved using residual fluorescence in the surgical cavity to determine the status of tumor margins. A total of three articles employed this method with complete available data, which resulted in a very limited sample size. The impact of individual studies was too significant, and the combined data from the three studies failed to provide sufficient statistical power, leading to instability and clinically meaningless results. Therefore, we did not include it in the quantitative analysis (29). Despite the high risk in the threshold criteria, we included the results of a study by Stubbs *et al.* in our quantitative analysis due to the comprehensive study design (24). We excluded Moore *et al.*'s study because of incomplete data extraction (23). In the heterogeneity analysis, when considering the close margin as either positive or negative for NIRF specimen imaging, the I^2 test results were 26% (95% CI: 0–100%) and 78% (95% CI: 52–100%). However, this heterogeneity was expected due to the different indicators involved. Considering the potential statistical bias from analyzing small datasets, we combined these data. The results of the heterogeneity analysis prompted us to select either a random or a mixed-effects model (35). When evaluating the status of HNC tumor surgical margins based on the fluorescence difference between post-operative tumor specimens and normal tissues, considering a close margin as positive or negative, both yielded wide CIs, probably due to the small sample size, leading to instability in the effect estimates. Under both criteria, the area under the SROC curve was 0.97 (95% CI: 0.95–0.98) and 0.99 (95% CI: 0.98–1.00), indicating a relatively robust result and a high diagnostic accuracy. Although our results indicate that NIRF imaging shows promise as a real-time method for evaluating HNC surgical margins, the 95% CIs for sensitivity and specificity are quite broad. This wide range suggests instability and unreliability in the results. Therefore, while the preliminary findings are encouraging, these results should be interpreted with caution in clinical applications.

When utilizing fluorescence in the surgical cavity to assess the surgical margin status, post-operative re-evaluation of the tumor bed using NIR ICG endoscopy aids in achieving clear margins because the wound bed should be ICG-negative after resection. In four studies with clearly recorded results, the sensitivity and specificity ranged from 33.33% to 100% and 85.71% to 100%, respectively, for detecting residual cancer cells in the tumor bed post-resection. Although this reflects a certain diagnostic capability, the lower sensitivity suggests challenges in identifying positive margins using this method. Low sensitivity may result in false negatives. Post-operative fluorescence in the surgical cavity/tumor bed did not conflict with specimen fluorescence. The operational difficulty and the time taken for surgery were manageable and acceptable. The relatively high specificity is advantageous for excluding non-disease cases and suggests that this technique can be used as an adjunct diagnostic tool after NIRF imaging (20).

Due to the presence of a threshold effect, DTA studies often exhibit greater heterogeneity than treatment/intervention studies (36). However, we did not observe statistically significant differences in the threshold effects. The Spearman correlation coefficient was calculated to evaluate the difference in fluorescence between tumor and normal tissues. The Spearman's rho for tumor tissues when the close margin was included as positive was −0.3441 (P=0.5563) and −0.5443, 0.6310 when the close margin was included as negative. Although in both situations, there was a negative correlation trend, the lack of statistical significance (large P values) suggests that this correlation might not be significant, likely due to the relatively small sample size. Further research with larger sample sizes, more detailed data collection, and alternative analytical methods is needed to comprehensively evaluate whether there is a threshold effect between sensitivity and specificity.

Studies by De Ravin *et al.* (16) and Fernandes *et al.* (37) suggest that NIRF imaging-guided surgery can facilitate real-time delineation of surgical margins during HNC surgery, improving margin clearance rates and enhancing progression-free survival. Our findings, to some extent, support their conclusions and further validate the utility in specific scenarios of HNC surgery. In this study, we strictly defined the use of NIRF to assess surgical margins and delineate tumor edges. While accurate delineation of tumors aids surgeons in precise localization and excision during surgery, it also serves as a foundational guide for determining surgical margins. Diagnostic assessment of the tumor margin status requires more precise quantitative standards and supportive outcomes.

Qualitative research

For clinical translation, an optimal fluorescent probe should have good distribution, high affinity for the target, and rapid clearance from the bloodstream, allowing for its effective accumulation at the tumor site and rapid acquisition of high-contrast images (38). ICG is a pioneering fluorescent dye used in fluorescence imaging-guided surgical procedures. It has demonstrated its capability through heightened permeability and retention effects, realizing the prospect of passive targeting for sentinel lymph node detection (39). Cetuximab and panitumumab, which are labeled with NIRF dyes, are two commonly employed probes that target the epidermal growth factor receptor (EGFR). The EGFR stands as one of the most pivotal targets, overexpressed in 80–90% of cases of head and neck squamous cell carcinoma (40). When employed in conjunction with fluorophores, they retain the capability to delineate HNC and lymph node metastases during fluorescence imaging-guided surgery for HNC. Targeted probes offer real-time intraoperative differentiation of the molecular boundaries between cancerous and adjacent normal tissues (41,42). In the included studies, irrespective of whether non-specific fluorescence, free (monomeric) ICG or its conjugates, or specific fluorescence was employed, panitumumab-IRDye800CW and cetuximab-IRDye800CW exhibited a heightened diagnostic capacity for the assessment of surgical margin status.

It is noteworthy that De Ravin *et al.* (16) demonstrated not only the feasibility of NIRF-guided HNC resection surgery but also its applicability to various tumor pathologies, primary sites, and surgical procedures. Our results validate this assertion.

Issues in the current practice

Histopathological assessment of biopsy tissue remains the gold standard for HNC diagnosis, although other imaging techniques can be used to complement lesion detection and staging. NIRF is considered a novel surgical adjunct tool that aids in preoperatively delineating surgical margins, potentially sparing patients from additional morbidity associated with extra surgery or chemoradiotherapy. However, their use in humans is limited by the scarcity of clinically approved fluorescent probes (43). In this study, only ICG received formal approval for clinical use, whereas the fluorescence-conjugated antibodies panitumumab-IRDye800CW and cetuximab-IRDye800CW are still in phase I/II clinical trials (33,44).

Precautionary measures must be taken when NIRF is used for surgical margin delineation. For instance, ICG may accumulate not only in cancerous tissues but also in inflammatory tissues and surgical trauma areas. This could potentially reduce the specificity of the initial stages of enhanced permeability and retention. These effects occur at much lower levels and are due to defects in lymphatic drainage structures. The applicability and safety of fluorescence-conjugated antibodies, such as panitumumab-IRDye800CW and cetuximab-IRDye800CW, in the human body require further optimization (33,38).

Although both the convenience of real-time tumor excision surgery guided by NIRF and the advantage of back-table NIRF imaging as an auxiliary modality over postoperative pathological methods are evident, our results support the high diagnostic capability of NIRF. However, relying solely on visual judgments remains challenging. The detection and identification of residual fluorescence within the surgical cavity solely by the naked eye are difficult (25). NIR imaging technology has proven to be a high-information, highly penetrating, and non-invasive prospective adjunctive treatment modality, and surgery guided by NIRF has demonstrated pathological effectiveness and applicability in preserving surgical margins in liver resection procedures (45-47). However, its application and trials in HNC are lacking. Numerous deficiencies are associated with the current model, and further clinical and preclinical research is required better to integrate this method into HNC management (48,49). Furthermore, different imaging schemes require more standardized criteria and comprehensive optimizations.

Study limitations

This systematic review and meta-analysis has certain limitations. As previously noted in the "Results" section, there is a moderate risk of publication bias, favoring better diagnostic accuracy in small-sample studies. Diminished statistical power may not detect the true presence of effects or lead to erroneous results. In cases where the number of included studies or patients is limited, it is challenging to assess the performance with a larger sample size and increased confidence. Furthermore, owing to data limitations, subgroup analyses for various diagnostic tests, such as different fluorophores, imaging times, or different thresholds, could not be performed. There are theoretical differences in the tissue distribution and NIRF imaging efficacy between specific and non-specific fluorophores. However, owing to the limited number of articles, we could only qualitatively describe the different studies without performing a combined analysis to obtain reliable results (16,50,51). Moreover, the standards for surgical tumor margins vary among different tumor sites and types. Since we could not obtain complete data, we had to use the margin standards of each study for the inclusion and analysis of the results rather than conducting further stratification or subgroup analysis (52,53). Moreover, constrained by different imaging systems and fluorophores, we opted against pooled analysis in the absence of sufficient data for subgroup analysis.

Other uses and future studies on NIRF in HNC

NIRF-guided surgery allows surgeons to achieve a visible contrast between normal and cancerous tissues. It provides high-resolution images, enabling the visualization of microscopic tumor nodules and with good tumor specificity owing to the targeting of exogenous drugs. One of the initial applications of NIRF imaging-guided surgery in humans was the injection of unbound ICG around a tumor for sentinel lymph node biopsy in HNC (54,55). The evolution of tumor-specific fluorescence imaging has enhanced the detection of metastases to regional lymph nodes, further improving the ability to detect lymphatic vessels in the area (56,57). Fluorescence imaging is employed to detect distant metastases of squamous cell carcinoma in the lungs. It is, therefore, a crucial tool for treating HNC because distant metastases are contraindications for surgical intervention. Both tumor and lymphatic metastases exhibit bright fluorescence emission, in distinct contrast with normal structures (58).

NIRF is also used to delineate the surgical margin by associating pathological diagnosis with visual impressions and assessing the differentiation between normal and cancerous tissues. There have been promising outcomes with fluorescence demarcation in NIRF-guided HNC surgery. Notably, van Keulen *et al.* reported the detection of secondary lesions, which are often overlooked by surgeons (59). Real-time fluorescence imaging-guided tumor resection, as demonstrated in their study, presents promising prospects.

In addition, the traditional approach of assessing tumor resection based on the surgeon's tactile feedback has been eliminated in transoral robotic surgery (TORS). TORS is preferred to open surgery because of its superior functional outcomes and low complication rates (60). In the future, more data-driven results may be needed to support the preference for TORS, which could be another crucial factor in supporting the use of NIRF-guided surgery (61). Furthermore, real-time imaging technology is particularly suited to support minimally invasive surgeries such as TORS, as they rely on video equipment to guide the surgical process. Real-time NIRF imaging greatly supports this need (62). Notably, with advances in artificial intelligence (AI), AI-based image augmentation, quantification, and optimization of video rates and imaging quality could reduce potential errors in assessing tumor surgical margins through visual evaluation using NIRF (63-66).

Conclusions

In this systematic review and meta-analysis, we identified seven studies describing the use of different fluorophores for the assessment of surgical margins in postoperative HNC specimens or surgical cavities. Quantitative research analysis has demonstrated the diagnostic accuracy and robust efficacy of NIRF in evaluating the status of surgical margins. Qualitative analysis further supports this conclusion. These results indicate that NIRF imaging is a promising approach for assessing or assisting in determining the status of surgical margins in HNC surgery. The prospects extend to the use of NIRF to assist various aspects of HNC surgery, as well as aid in TORS. This diagnostic assistance is beneficial and may contribute to positive outcomes in the assessment of HNC surgical margins, thereby enhancing overall surgical effectiveness.

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Footnote

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