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Novel imaging techniques for intraoperative margin assessment in surgical oncology: A systematic review

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Abstract

Inadequate margins continue to occur frequently in patients who undergo surgical resection of a tumor, suggesting that current intraoperative methods are not sufficiently reliable in determining the margin status. This clinical demand has inspired the development of many novel imaging techniques that could help surgeons with intraoperative margin assessment. This systematic review provides an overview of novel imaging techniques for intraoperative margin assessment in surgical oncology, and reports on their technical properties, feasibility in clinical practice and diagnostic accuracy. PubMed, Embase, Web of Science and the Cochrane library were systematically searched (2013-2018) for studies reporting on imaging techniques for intraoperative margin assessment. Patient and study characteristics, technical properties, feasibility characteristics and diagnostic accuracy were extracted. This systematic review identified 134 studies that investigated and developed 16 groups of techniques for intraoperative margin assessment: fluorescence, advanced microscopy, ultrasound, specimen radiography, optical coherence tomography, magnetic resonance imaging, elastic scattering spectroscopy, bio-impedance, X-ray computed tomography, mass spectrometry, Raman spectroscopy, nuclear medicine imaging, terahertz imaging, photoacoustic imaging, hyperspectral imaging and pH measurement. Most studies were in early developmental stages (IDEAL 1 or 2a, n = 98); high-quality stage 2b and 3 studies were rare. None of the techniques was found to be clearly superior in demonstrating high feasibility as well as high diagnostic accuracy. In conclusion, the field of imaging techniques for intraoperative margin assessment is highly evolving. This review provides a unique overview of the opportunities and limitations of the currently available imaging techniques.

KEYWORDS
cancer, medical imaging, surgical margin, surgical oncology, systematic review

1 | INTRODUCTION

Surgical resection remains the cornerstone of therapy for patients with primary solid tumors.[1] The objective of surgical oncology is complete resection of the tumor with adequate, that is, clear, margins. At

Abbreviations: CT, computed tomography; ESS, elastic scattering spectroscopy; FSA, frozen section analysis; IDEAL, idea, development, exploration, assessment, long-term study; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

Jan Heidkamp and Mirre Scholte contributed equally to this study.

the same time, very radical approaches are considered undesirable in many organs because of related morbidity, loss of function and esthetics.

Achieving adequate resection margins is a critical element of surgical oncology, as inadequate resection margins are associated with increased recurrence rates and poorer survival.[2-7] Furthermore, inadequate margins put patients at risk of undergoing additional therapy, that is, re-resection or adjuvant (chemo) radiotherapy, which is associated with increased morbidity, reduced quality of life and costs.[8-19] Despite the burden on patients and the healthcare system, inadequate margins continue to occur frequently in around 5% of resections of lung[4] and kidney[20] tumors, in 15% to 20% of resections of breast,[2] prostate[21] and rectal[6] cancer and in up to 40% and 60% of resections of vulvar[22] and oral[5] cancer.

These incidence rates illustrate that the currently employed methods for intraoperative decision-making on which surgeons still mainly rely, that is, tactile and visual feedback, are not sufficiently reliable in determining the margin status. Frozen section analysis (FSA), in which parts of the resected specimen or surgical cavity are quick-frozen and sectioned for histopathological analysis, is also not an ideal strategy for intraoperative margin assessment. Although this technique has high accuracy, its diagnostic value in the detection of inadequate margins is limited due to sampling error.[23-29] Furthermore, it is time consuming and costly.[24,25,29] Definitive histopathological assessment by the pathologist, which is the gold standard, usually takes several days to a week to obtain and can therefore not inform intraoperative decision-making. There seems a clinical need for intraoperative methods that ideally could (a) delineate the tumor margin within the surgical field just before and/or during the resection of the malignancy; (b) assess the surgical cavity enabling immediate re-section of any residual tumor and (c) assess the resection margin of the surgical specimen enabling an immediate re-resection should that be necessary (Figure 1).

To reduce the number of inadequate margins and associated consequences, there has been wide interest in imaging techniques for intraoperative margin assessment.[30,31] Given the plethora of techniques in both early and late developmental stages, it is troublesome for surgeons to select one that could meet their specific needs. The aim of this systematic review therefore is to provide an overview of novel imaging techniques for intraoperative margin assessment and to report their technical properties, feasibility in clinical practice and diagnostic accuracy.

> **What's new?**
>
> While surgical resection is critical in the treatment of primary solid tumors, resection at tumor margins remains problematic, with inadequately resected margins facilitating tumor recurrence. In this systematic review, the authors collected information on novel imaging techniques applied to the intraoperative assessment of tumor margins across cancer types. A total of 16 groups of techniques were identified, with many in early stages of clinical application. Following comparison, no single technique was clearly superior in clinical feasibility or diagnostic accuracy. The review highlights the evolving nature of imaging techniques for intraoperative margin assessment and identifies opportunities and limitations in the field.

2 | METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[32] Additional information on the methods used in this systematic review can be found in Supplementary 1.

2.1 | Search strategy

PubMed, Embase, Web of Science and Cochrane library databases were systematically searched for studies that investigated an imaging technique with the aim of intraoperative margin assessment. The search query, which was composed in consultation with an information specialist, combined synonyms for margins of excision, diagnostic imaging (including frequently used imaging techniques) and histology

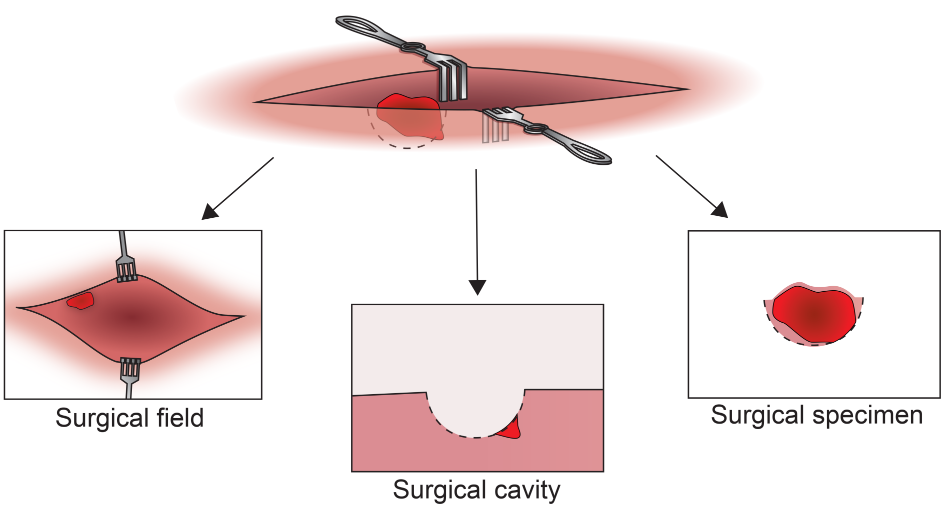

FIGURE 1 The three areas of interest at which imaging techniques could assist surgeons with intraoperative margin assessment: the surgical field, the cavity and the specimen [Color figure can be viewed at wileyonlinelibrary.com]

(Supplementary 1). Articles published from January 2013 to December 2018 were included. No language restriction was imposed.

2.2 | Study selection

Two authors (J. H., M. S.) independently reviewed the retrieved citations for potential eligibility by screening the titles and abstracts, and the full text was sought for any citation identified for potential inclusion. Any disagreements were solved by discussion with a third author (M. M. R.). Studies were included that presented original study data on the use of an imaging technique with the aim for intraoperative margin assessment in human subjects with histopathology as reference standard.

2.3 | Data extraction and quality assessment

Using a predefined form, two authors (J. H., M. S.) independently extracted data on patient and study characteristics, technical properties of the imaging technique, criteria describing the feasibility of the imaging technique in clinical practice and its diagnostic accuracy (for an overview of all extracted items, see Supplementary 1). The risk of bias and applicability of the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) scoring system.[33] Two authors (J. H., M. S.) independently performed the quality assessment and any disagreements were resolved by consulting with a third author (M. M. R.).

2.4 | Data synthesis

2.4.1 | Patient and study characteristics

Patient and study characteristics included country of origin, IDEAL-stage,[34] sample size, cancer type and T-classification, surgical technique, imaging technique and area of interest (the surgical specimen, surgical cavity or surgical field; Figure 1). The techniques were categorized according to the underlying physical mechanism/principle. The IDEAL framework describes the stages of innovation in surgery (idea, development, exploration, assessment and long-term study).[34] This method was adopted to provide insight into the developmental stage of the investigated imaging technique.

2.4.2 | Technical properties

Technical properties comprised scanning area/volume (mm^2/mm^3), resolution (mm) acquisition time (minutes) and penetration depth (mm). Techniques were classified into surface and subsurface technique to differentiate between two-dimensional (mm^2) and three-dimensional (mm^3) scanning areas, and complete or partial scanning of the area of interest. This resulted in four groups of techniques: those that scanned (a) the complete surface of interest; (b) part(s) of the surface of interest; (c) the complete subsurface of interest or (d) part(s) of the subsurface of interest.

2.4.3 | Feasibility in clinical practice

Criteria describing the feasibility of the imaging technique in clinical practice were adapted from Ha et al[35] and were scored "yes," "no," or "-" for not reported. Criteria were continuous feedback to the surgeon, resolution comparable to histopathology, scanning of the entire area of interest, scanning within intraoperative timescale, translation of the obtained information to an intraoperative action, subsurface information and non-destructiveness.

2.4.4 | Diagnostic accuracy

Data from each study were summarized in contingency tables of true-positive, false-positive, true-negative, false-negative findings; calculated sensitivity, specificity, and positive predictive and negative predictive values. We distinguished between feasibility studies assessing samples of tumor vs normal tissue and proof-of-concept studies that calculated diagnostic accuracy on margin assessment (ie, detection of adequate vs inadequate margins). We further differentiated inadequate margins as either positive margins or positive and close margins.

3 | RESULTS

3.1 | Systematic search

The search strategy yielded 2995 unique records, of which 134 met the eligibility criteria after title and abstract review, and subsequent full text review (Figure 2).

Additional results can be found in Supplementary 2.

3.2 | Quality assessment

Overall, the quality of included studies varied (Supplementary 2: Figures 1 and 2). For the patient selection domain most studies had unclear (n = 69, 51%) or high (n = 41, 30%) risk of bias. Most studies had low risk of bias for the imaging technique (n = 78, 58%), reference standard (n = 111, 83%), and flow and timing (n = 83, 62%) domains (Supplementary 2: Table 1). Study quality seemed to be dependent on the IDEAL stage, as stage 3 studies had higher overall quality than studies in other stages (Supplementary 2: Figures 3-7). In general, applicability concerns were low.

3.3 | Patient and study characteristics

The number of publications increased each year (Figure 3; Supplementary 2: Table 2). Most studies originated from the USA (n = 53; 40%), followed

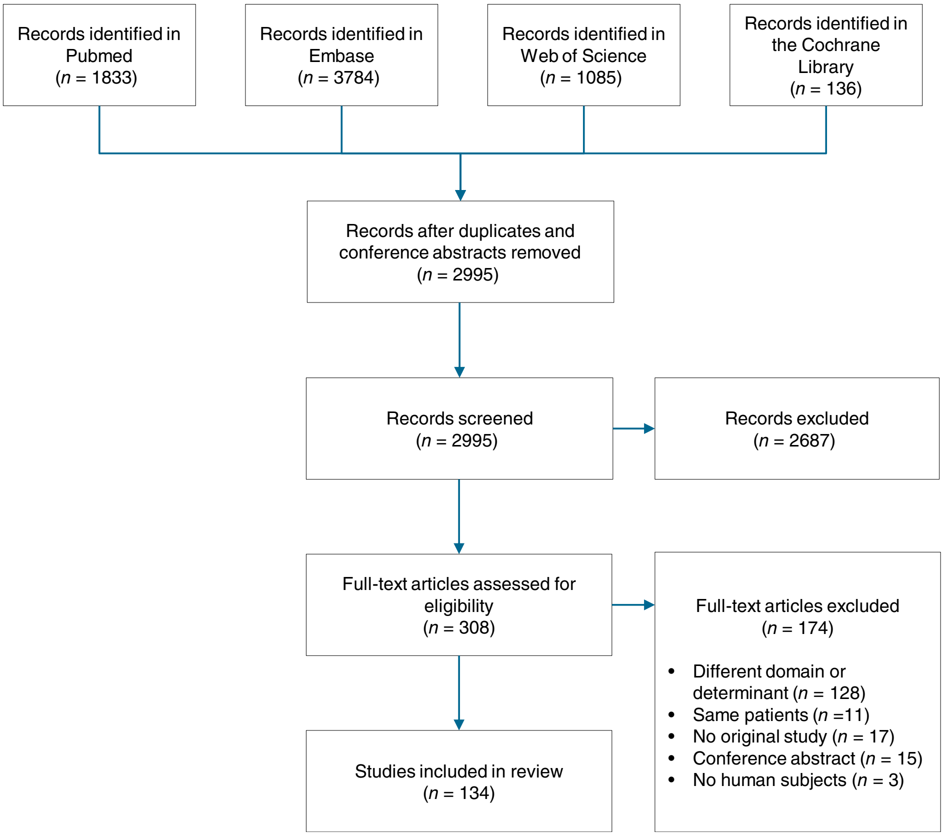

FIGURE 2 PRISMA flowchart [Color figure can be viewed at wileyonlinelibrary.com]

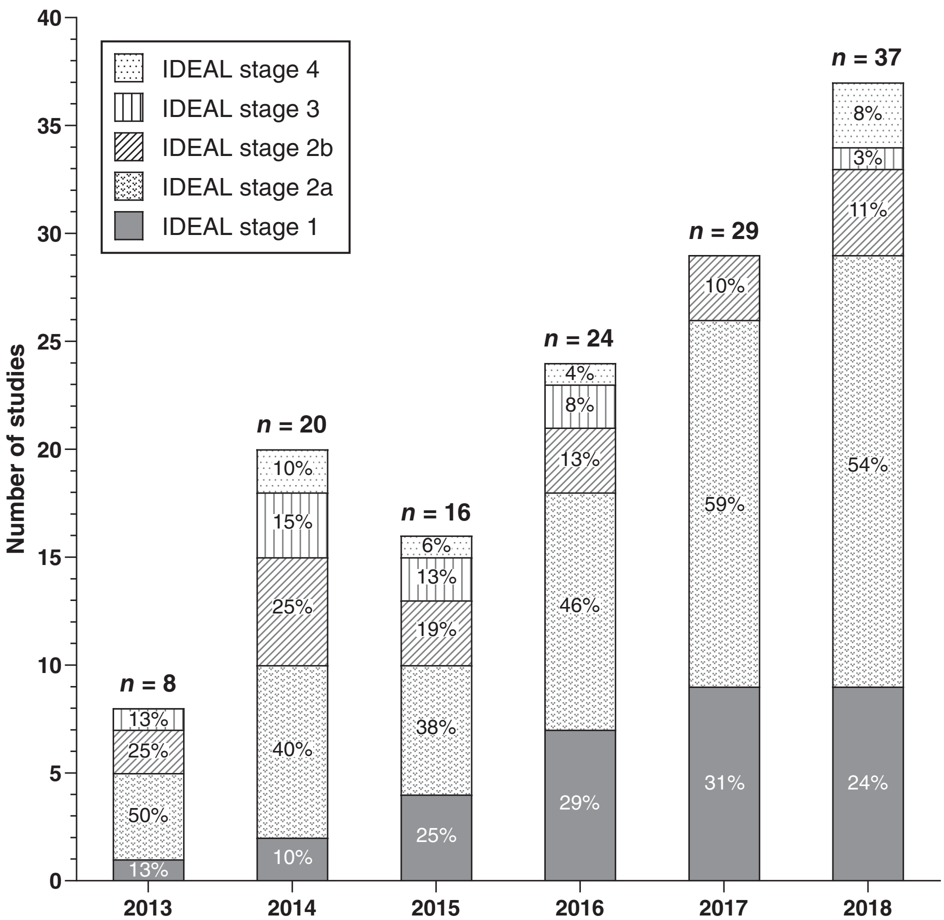

FIGURE 3 Number of publications per year (displayed above each column) stratified per IDEAL-stage (percentages within the columns). The number of publications increased each year, which was mainly driven by the increasing portion of studies in the IDEAL 1 and 2a stage. The portions of stage 2b and 3 remain relatively small over the years

by the Netherlands (n = 14; 10%) and Germany (n = 11; 8%) (Supplementary 2: Table 3). Half of the studies (n = 67) were conducted in breast cancer surgery (Supplementary 2: Table 4). The median number of included patients was 23 (range, 1-842); five (4%) studies did not report the number of included patients. The majority of studies included patients that had received treatment for primary disease, while seven (5%) studies (partly) included patients with metastatic disease. Open surgery was performed in most studies (n = 100; 75%), seven (5%) studies employed a laparoscopic approach, eight (6%) employed either a laparoscopic or an open approach and 19 (14%) studies did not mention the surgical approach. Most techniques (n = 108) assessed the surgical specimen, simultaneous assessment of all three areas of interest was most frequently (n = 7) done with a fluorescence technique (Figure 4; Supplementary 2: Table 5). Most included studies investigated a technique in the early stage of development (IDEAL 1 to 2a) (Figure 3; Supplementary 2: Table 6). The majority (n = 66, 49%) of studies were in IDEAL 2a, that were nonrandomized studies and did not yet use the outcomes of the imaging technique for intraoperative decision-making. In total, 16 technique categories were identified: fluorescence (n = 32), advanced microscopy (n = 18, for definition, see Supplementary 2), ultrasound (n = 17), specimen radiography (n = 13), and optical coherence tomography (OCT, n = 13), magnetic resonance imaging (MRI, n = 10), elastic scattering spectroscopy (ESS, n = 8), bio-impedance (n = 6), X-ray computed tomography (CT, n = 6), mass spectrometry (n = 5), Raman spectroscopy (n = 5), nuclear medicine imaging (n = 3), terahertz imaging (n = 3), photoacoustic imaging (n = 2), hyperspectral imaging (n = 1) and pH measurement (n = 1) (Supplementary 2: Table 7). Characteristics of each study are summarized and stratified per imaging category in Supplementary Table 1.

3.4 | Technical properties

Technical properties of the investigated techniques are summarized and stratified per imaging category in Supplementary Table 2. Only 44 of 134 studies reported all technical properties, that is, resolution, scanned area or volume, and acquisition time (Figure 5). In general, techniques scanning a surface of the area of interest achieved higher resolutions than techniques scanning a three-dimensional volume, that is, subsurface techniques. Subsurface techniques more often scanned the whole area of interest compared to the surface

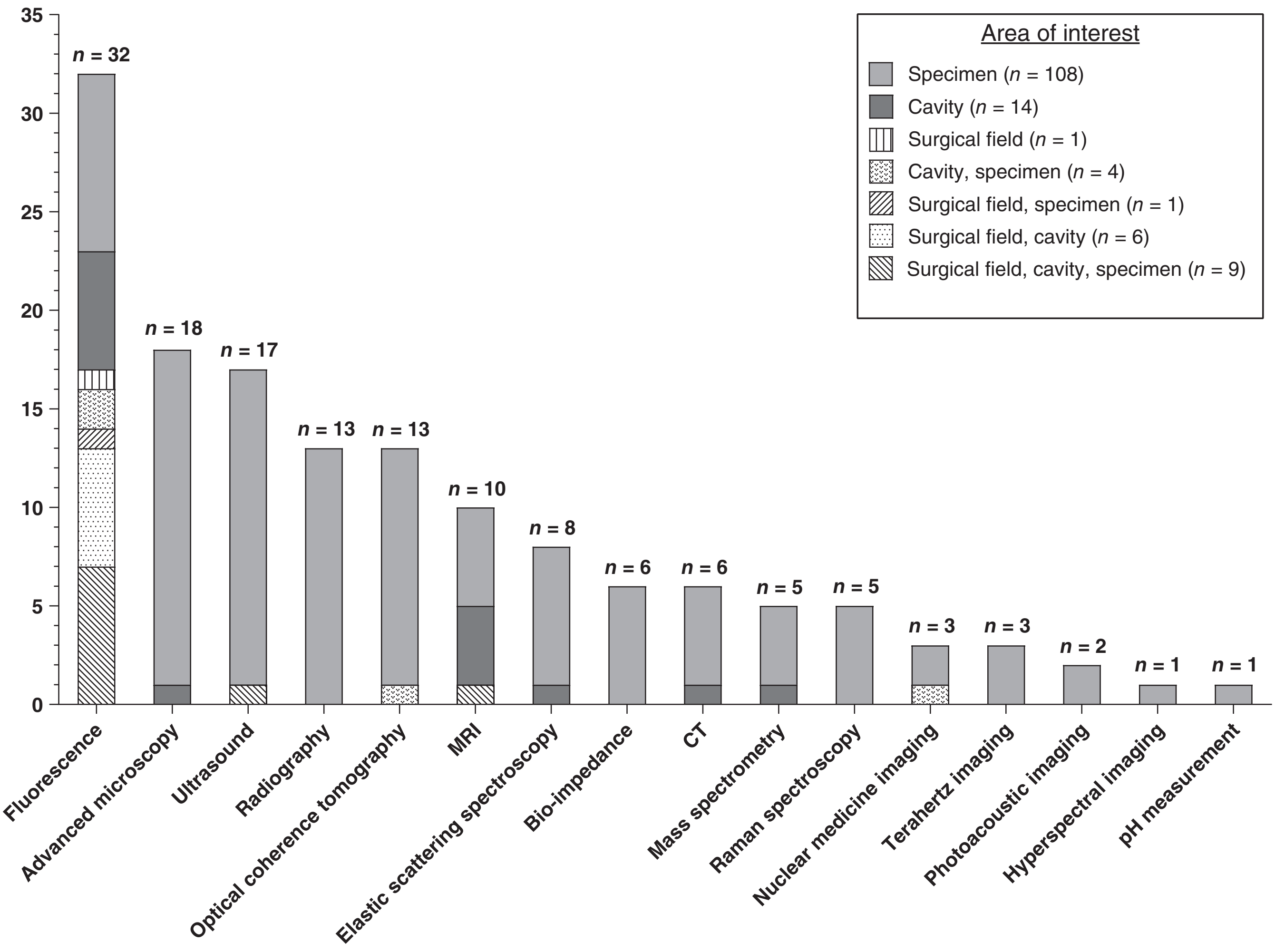

FIGURE 4 The number of studies (displayed above each column) per group of imaging technique stratified per area of interest. Studies investigating two techniques were included in the figure twice

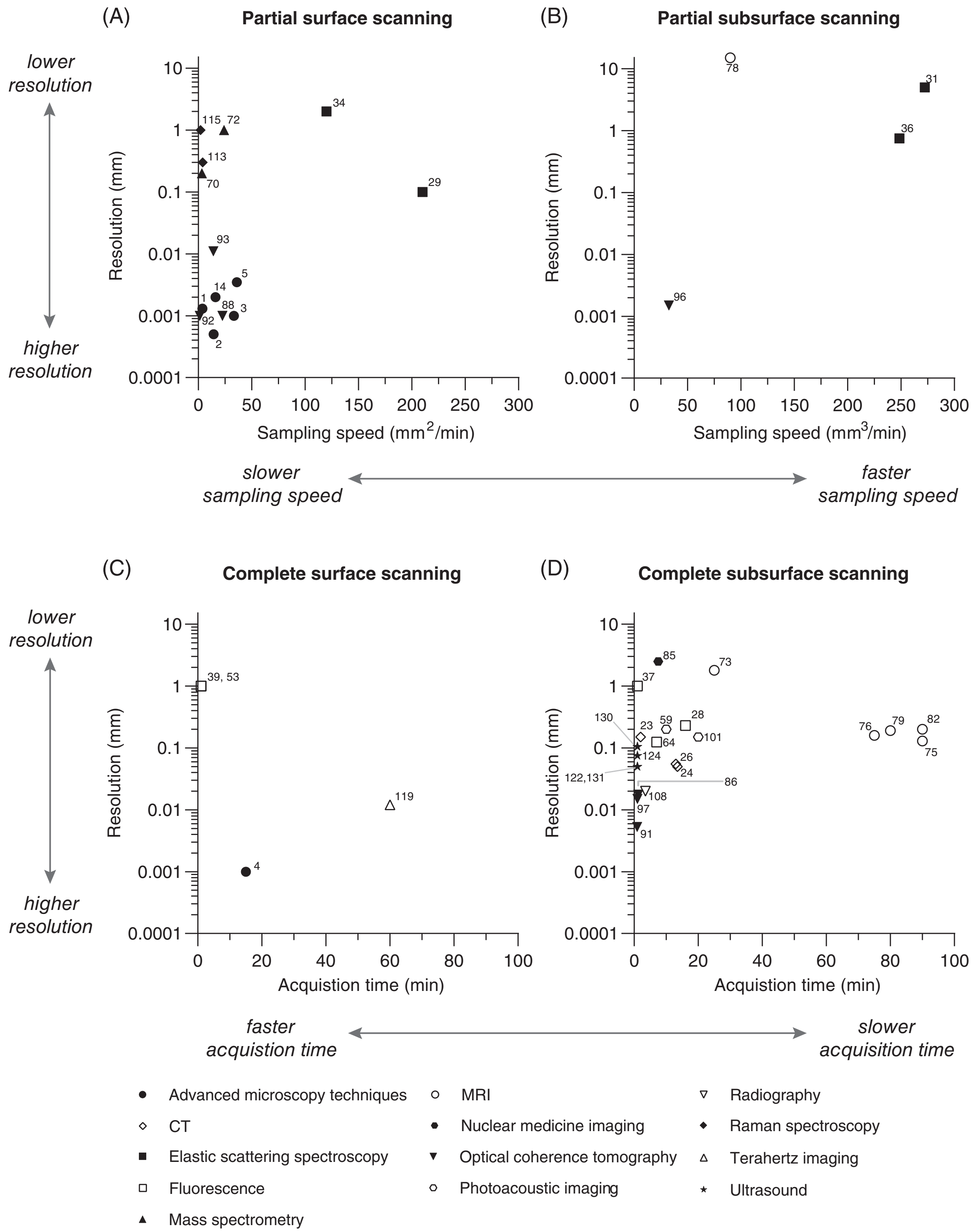

FIGURE 5 The relation between resolution and acquisition time. Four groups were distinguished with (A), studies that scanned part(s) of the surface, (B) part(s) of the subsurface, (C) the complete surface and (D) the complete subsurface. The numbers provided with each symbol refer to the original studies as displayed in Supplementary Table 2

techniques. For the surface techniques, advanced microscopy and OCT provided both a relatively high resolution as well as generally short acquisition times. ESS achieved relatively low resolutions, but high sampling speed. For the subsurface techniques, OCT, ultrasound, CT and radiography provided relatively high resolutions at short acquisition times.

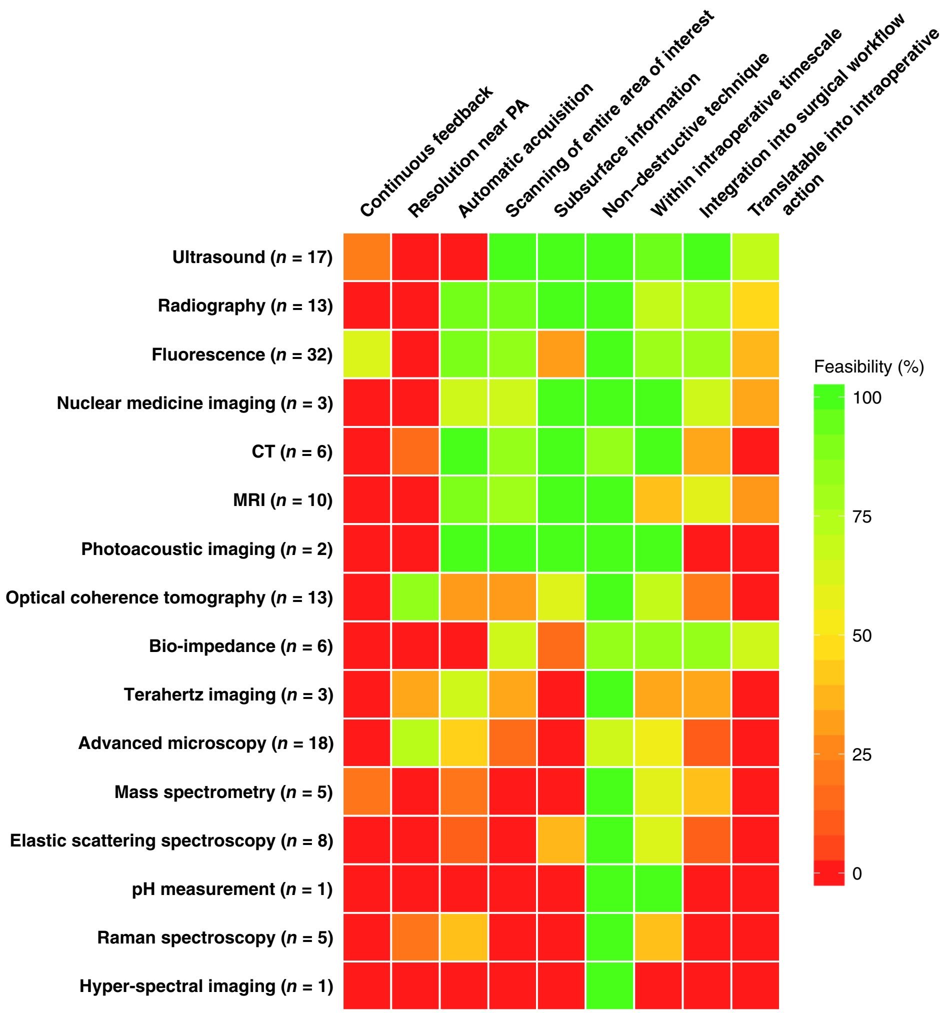

FIGURE 6 Overview of feasibility in clinical practice summarized per imaging category and sorted from highest to lowest feasibility. The number of studies per imaging category scoring a "yes" was obtained from Supplementary Table 3 and expressed as a percentage for each individual feasibility criterion. The total number of studies per imaging category is displayed between parentheses [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Feasibility in clinical practice

The criteria scoring feasibility of techniques in clinical practice are summarized and stratified per imaging category in Supplementary Table 3. Ultrasound, radiography and fluorescence scored the highest feasibility (Figure 6). Nuclear medicine imaging, CT, MRI, photoacoustic imaging, OCT, bio-impedance, terahertz imaging, advanced microscopy, mass spectrometry and ESS showed moderate feasibility. pH measurement, Raman spectroscopy and hyperspectral imaging scored relatively low feasibility.

3.6 | Diagnostic accuracy

Fifty-nine (44%) of 134 studies reported diagnostic accuracy (Supplementary Table 4). Twenty-six of 59 studies were feasibility studies reporting diagnostic accuracy in detection of tumor vs normal tissue samples (Supplementary Table 4a). The other 33 studies were proof-of-concept studies which assessed the diagnostic accuracy on margin assessment in patients (Supplementary Table 4b). Ten of these studies reported diagnostic performance in detection of inadequate, that is, positive, margins, of which two used a surface scanning technique and eight a technique that provided subsurface information. For mass spectrometry, ESS, OCT, radiography and ultrasound, at least one study reported high diagnostic accuracy. Twenty-three studies reported on the diagnostic accuracy in assessing inadequate, that is, positive and close, margins. Out of these 23, 21 studies used a subsurface technique, one used a surface scanning technique, and in one study, it was unknown whether the technique provided subsurface information. For bio-impedance, fluorescence, OCT, photoacoustic imaging, radiography and ultrasound, at least one study demonstrated high diagnostic accuracy. Overall, there were moderate to large differences in reported diagnostic accuracy of studies investigating the same technique. For example, while both investigated OCT in breast cancer, Erickson-Bhatt et al[36] scored 92% sensitivity and 92% specificity while Zysk et al[37] scored 63% sensitivity and 37% specificity.

4 | DISCUSSION

4.1 | Summary of main findings

This systematic review of the technical properties, feasibility in clinical practice and diagnostic accuracy of novel imaging techniques for intraoperative margin assessment revealed that 16 groups of techniques are currently under development and investigation: fluorescence (n = 32), advanced microscopy (n = 18), ultrasound (n = 17), specimen radiography (n = 13), OCT (n = 13), MRI (n = 10), ESS (n = 8), bio-impedance (n = 6), CT (n = 6), mass spectrometry (n = 5), Raman spectroscopy (n = 5), nuclear medicine imaging (n = 3), terahertz imaging (n = 3), photoacoustic imaging (n = 2), hyperspectral imaging (n = 1) and pH measurement (n = 1). Our results showed that 73% (n = 66) of techniques were in the early stages of research and development, that is, IDEAL stages 1 and 2a. Surprisingly, also for more conventional techniques, such as radiography, high-quality stage 2b and 3 studies were underrepresented. The majority (n = 100; 75%) of techniques were applied in open surgical procedures and most studies (n = 108) assessed margins on the resection specimen. One fourth of all studies (n = 33) reported diagnostic accuracy on margin assessment, with sensitivities ranging from 21% to 100% and specificities from 37% to 100%. None of the techniques assessed in this review appeared to be clearly superior by demonstrating both high feasibility and diagnostic accuracy.

4.2 | Strengths and limitations

This is the first study systematically investigating imaging techniques for intraoperative margin assessment across all types of cancer. Several other studies focused on a specific type of imaging or cancer, or did not systematically search the literature.[23,30,31,38-41] Our study has a broad scope to encourage the interdisciplinary exchange of knowledge. Furthermore, this systematic review offers a framework to evaluate available (and future) techniques according to the same criteria. Although early stage technologies are often still under development, which means that their technical properties, feasibility and diagnostic accuracy continue to improve, it is essential to compare them to mature techniques as it helps revealing promising features and areas for improvement. Finally, this review could assist surgeons in selecting imaging techniques for intraoperative margin assessment that meet their specific needs and may subsequently guide research and development of promising techniques.

Some limitations should also be discussed. First, as we limited our search period, that is, from 2013 to 2018, we might have missed potentially promising techniques that reached the end of their developmental stage before 2013. However, we consider this a small risk, since no imaging technique for intraoperative margin assessment is currently widely applied in clinical practice and since this review identified such a large number of techniques in early developmental stages. Second, not all of the reviewed imaging techniques could be studied in full detail, as two third of the included studies lacked important details on technical properties and only one fourth of the included studies reported diagnostic accuracy on margin assessment. Third, multiple studies investigated the same imaging technique in the same type of tumor, for example, radiography and ultrasound in breast cancer. However, due to the large heterogeneity in patient populations and definition of inadequate margins between studies, it was not possible to conduct a meta-analysis.

4.3 | Clinical implications

Radiography and ultrasound were found to be the most mature techniques (ie, highest number of IDEAL 3 and 4 studies), mainly for use in breast cancer. Despite their high feasibility scores, a broad clinical implementation in breast cancer surgery is probably unlikely as they showed low diagnostic accuracy. Radiography and ultrasound were only sparsely applied in other cancer types.

Intraoperative fluorescence was the most frequently investigated technique, but studies were exclusively in IDEAL stages 1 and 2. It was applied in multiple cancer types for delineation of the tumor margin in the surgical field, inspection of the surgical cavity and the resection specimen. Apart from its high feasibility, a unique strength of fluorescence is the ability to provide real-time feedback to the surgeon. The limited—wavelength-dependent—penetration depth (<10 mm) of fluorescence makes its application in the localization of deeper-seated tumors, such as breast cancer and sarcomas, unlikely.[30,31] The transition from use of nontargeted to targeted fluorescent probes is expected to increase the technique's diagnostic accuracy, but clinical implementation is slow as the development of these agents is subject to extensive regulations.[42] Fluorescence therefore is a highly promising technique with multiple ongoing studies, but considering its challenges at this stage, cannot yet be considered a mature technique ready for broad implementation in clinical practice.

The application of CT, OCT and MRI for intraoperative margin assessment is relatively new. These methods were frequently investigated and scored above-average for feasibility in clinical practice. In contrast with fluorescence, these techniques are more focused on margin assessment of the resection specimen (ex vivo). All three techniques acquire cross-sectional anatomical images of tissue, and, unlike fluorescence techniques, do not necessarily rely on contrast agents. The penetration depth of OCT is limited, typically between 1 and 3 mm,[43] but OCT can produce images using a handheld device with a resolution close to histology. CT and MRI, on the other hand, are not portable devices and achieve automated image acquisition at resolutions typically below 1 mm. Compared to CT, MRI has a superior soft-tissue contrast, but comes with the disadvantage of relatively long acquisition times. These techniques provide an interesting upcoming alternative to fluorescence, yet they require further improvement regarding "integration into surgical practice" and "translation into intraoperative action," and diagnostic accuracy.

Meanwhile, the very novel and innovative imaging techniques that scored low on feasibility and diagnostic accuracy should not be dismissed as this field is highly evolving. Examples are techniques such as ESS and Raman spectroscopy, which employ the interaction of light with tissue to obtain optical and biochemical fingerprints for tissue characterization. These techniques scored low on feasibility and were limited by their slow acquisition time and by not being able to sample the entire margin. These technical hurdles need to be overcome, before surgical care for cancer patients could benefit from these techniques that are sensitive to the microarchitectural and molecular changes of cancerous tissue.[44-46] Another technique that scored low feasibility, yet demonstrated a very innovative surgical workflow, is the near real-time characterization by mass spectrometry of aerosols released during electrosurgical dissection.[47] Novel and innovative applications are also being developed in the more established field of fluorescence. For instance, optical specimen mapping to uniquely quantify and evaluate resection margins of tumor specimens obtained from patients previously infused with a tumor-targeted fluorescent dye.[48]

Given the plethora of available techniques, a recommendation regarding the most valuable and promising technique(s) would have been helpful. This review found little evidence, however, to recommend any of the available techniques as promising for clinical practice, which is due to the early developmental stage of most studies. While being essential for demonstrating feasibility, early development studies are insufficient to justify the clinical merits on a broad scale. However, the framework established in this review, which evaluated each technique according to same set of parameters and criteria, may help in the selection and evaluation of (future) imaging techniques.

Considering the different types of cancer, different standard practices for surgical oncological care and even different personal preferences of surgeons, it is impossible to establish a general set of minimal requirements that imaging techniques must meet before they are acceptable for intraoperative margin assessment. We believe that the starting point for the selection of an appropriate technique should be current standard of care, as it determines the minimal requirements and opportunities for improvement. For example, if FSA is currently used for intraoperative margin assessment, the new technique should at least be as accurate as FSA and, at the same time, should improve its slow acquisition times.

The added value of imaging techniques for intraoperative margin assessment is indication dependent. To further illustrate this, we will discuss three examples of oncologic resections that require a dedicated surgical approach, and therefore specific imaging technique requirements. First, we discuss the setting of resections that allow a wide radical intent, for example, colon and liver cancer. In this type of resection, the erroneous removal of healthy tissue would minimally affect the quality of life of patients. A suitable imaging technique in this context would require high sensitivity to detect tumor margins, while specificity is less important as false positive outcomes have limited consequences, that is, erroneous removal of healthy tissue does not majorly affect patient's functionality or esthetics. Single time feedback to the surgeon would be sufficient as this resection bears a relatively low risk of inadequate margins. Second, in resections that do not allow a wide radical intent, for example, rectal, vulvar, and head and neck cancer, a too radical approach would directly confront patients with the consequences of functional morbidity and impaired esthetics. A suitable imaging technique here would require high sensitivity and specificity for accurate margin detection. Furthermore, visualization of surrounding anatomical structures and multiple moments of intraoperative feedback are important to (continuously) monitor tumor resection in relation to critical structures. Third, in the setting of resections where it is required for the tumor to remain untouched and intact due to the high risk of seeding of cancer cells, for example, cancer of the pancreas and soft-tissue sarcoma. A suitable imaging technique would require high sensitivity for detecting margins and continuous subsurface information of the tumor location within the surgical field to ensure that the surgeon does not cut through the tumor and tumor integrity is maintained.

4.4 | Implications for future research

As demonstrated by the large number of studies in our review, it seems that a technology push has driven the development of novel imaging techniques for intraoperative margin assessment. Since research resources are limited, it is not feasible, let alone desirable, to investigate all techniques for all types of cancer. Therefore, the indications that have the greatest need for novel technology for intraoperative margin assessment should be identified, so that promising imaging techniques can subsequently be matched to these indications. Ideally, research should be focused on promising techniques for indications where improvement in intraoperative margin assessment can be expected and is needed.

In many of the included studies, important details were not reported which implied that they could not be studied comprehensively. In a broader sense, the lack of details hampers a fair comparison of techniques and their clinical assessment. Moreover, we found moderate to large differences in diagnostic accuracy between studies investigating the same technique. This can potentially be attributed to differences in study quality, study design, IDEAL stage and tumor type. We therefore emphasize the importance of reporting guidelines and the use of frameworks such as IDEAL that provide guidance on how to conduct research in each developmental stage. The framework presented in this review could help in reporting the characteristics of investigated imaging techniques in a more standardized and uniform manner.

High-quality IDEAL stage 2b and 3 studies were generally lacking which can be expected for imaging techniques that are currently under development. Surprisingly, however, for the more familiar techniques, such as fluorescence, ultrasound and radiography, IDEAL stage 3 studies were also underrepresented. This is a notable finding as the true benefit of a technique is preferably studied in phase 3 randomized diagnostic trials. In these trials, diagnostic accuracy, but more importantly the impact on patient outcomes can be studied. This is essential, as diagnostic tests alone do not improve patient outcomes. Only when diagnostic accuracy is combined with effective treatment options (ie, resection of tumor or sparing of healthy tissue), important outcomes such as quality of life, disease-free survival and overall mortality can be studied.

5 | CONCLUSION

The field of imaging techniques for intraoperative margin assessment is highly evolving. This review provides a unique overview of the opportunities and limitations of the currently available imaging techniques. Considering the plethora of available techniques, a recommendation regarding the most valuable and promising technique(s) would have been helpful. The current evidence, however, mostly originates from studies in early developmental stages and therefore does not support the recommendation of any specific technique to clinical practice. The comparison of all techniques within one framework could assist surgeons in selecting imaging techniques for intraoperative margin assessment that meet their specific needs and may subsequently guide research and development of promising techniques.

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CONFLICT OF INTEREST

J. J. F. reports grants from Profound Medical during the conduct of this study and grants from Siemens Healthineers outside the submitted work. M. M. R. reports that Siemens Healthineers has provided some grants to perform research on imaging in surgery. This money was paid for the institute and there were no restrictions regarding publications or data. All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in this study, and data sources and handling of these data are described in the Section 2 and in the Supporting Information. Further information is available from the corresponding author upon request.

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REFERENCES

1. Sullivan R, Alatise OI, Anderson BO, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncol*. 2015;16:1193-1224.
2. Houssami N, Macaskill P, Luke Marinovich M, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. 2014;21:717-730.
3. Yossepowitch O, Briganti A, Eastham JA, et al. Positive surgical margins after radical prostatectomy: a systematic review and contemporary update. *Eur Urol*. 2014;65:303-313.
4. Hancock JG, Rosen JE, Antonicelli A, et al. Impact of adjuvant treatment for microscopic residual disease after non-small cell lung cancer surgery. *Ann Thorac Surg*. 2015;99:406-413.
5. Smits RWH, Koljenović S, Hardillo JA, et al. Resection margins in oral cancer surgery: room for improvement. *Head Neck*. 2016;38(suppl 1):E2197-E2203.
6. Simillis C, Baird DLH, Kontovounisios C, et al. A systematic review to assess resection margin status after abdominoperineal excision and pelvic exenteration for rectal cancer. *Ann Surg*. 2017;265:291-299.
7. Stojadinovic A, Leung DHY, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. *Ann Surg*. 2002;235:424-434.
8. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol*. 2014;32:1507-1515.
9. Talsma AK, Reedijk AMJ, Damhuis RAM, Westenend PJ, Vles WJ. Re-resection rates after breast-conserving surgery as a performance indicator: introduction of a case-mix model to allow comparison between Dutch hospitals. *Eur J Surg Oncol*. 2011;37:357-363.
10. Harji DP, Griffiths B, Velikova G, Sagar PM, Brown J. Systematic review of health-related quality of life issues in locally recurrent rectal cancer. *J Surg Oncol*. 2015;111:431-438.
11. The American Society of Breast Surgeons. Consensus guideline on breast cancer lumpectomy margins. December 20, 2017.
12. Wang EH, Corso CD, Rutter CE, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer. *J Clin Oncol*. 2015;33:2727-2734.
13. Parvez Shaikh M, Alite F, Wu MJ, Solanki AA, Harkenrider MM. Adjuvant radiotherapy versus wait-and-see strategy for pathologic T3 or margin-positive prostate cancer: a meta-analysis. *Am J Clin Oncol*. 2018;41:730-738.
14. Langendijk JA, Ferlito A, Takes RP, et al. Postoperative strategies after primary surgery for squamous cell carcinoma of the head and neck. *Oral Oncol*. 2010;46:577-585.
15. Chapman BV, Gill BS, Viswanathan AN, Balasubramani GK, Sukumvanich P, Beriwal S. Adjuvant radiation therapy for margin-positive vulvar squamous cell carcinoma: defining the ideal dose-response using the national cancer data base. *Int J Radiat Oncol Biol Phys*. 2017;97:107-117.
16. Borschitz T, Gockel I, Kiesslich R, Junginger T. Oncological outcome after local excision of rectal carcinomas. *Ann Surg Oncol*. 2008;15:3101-3108.
17. Savard J, Ivers H. The evolution of fear of cancer recurrence during the cancer care trajectory and its relationship with cancer characteristics. *J Psychosom Res*. 2013;74:354-360.
18. Hong YM, Hu JC, Paciorek AT, Knight SJ, Carroll PR. Impact of radical prostatectomy positive surgical margins on fear of cancer recurrence: results from CaPSURE. *Urol Oncol*. 2010;28:268-273.
19. Sharma N, Purkayastha A. Impact of radiotherapy on psychological, financial, and sexual aspects in postmastectomy carcinoma breast patients: a prospective study and management. *Asia Pac J Oncol Nurs*. 2017;4:69-76.
20. Marszalek M, Carini M, Chlosta P, et al. Positive surgical margins after nephron-sparing surgery. *Eur Urol*. 2012;61:757-763.
21. Sooriakumaran P, Srivastava A, Shariat SF, et al. A multinational, multi-institutional study comparing positive surgical margin rates among 22 393 open, laparoscopic, and robot-assisted radical prostatectomy patients. *Eur Urol*. 2014;66:450-456.
22. Te Grootenhuis NC, Pouwer AW, de Bock GH, et al. Margin status revisited in vulvar squamous cell carcinoma. *Gynecol Oncol*. 2019;154:266-275.
23. St John ER, Al-Khudairi R, Ashrafian H, et al. Diagnostic accuracy of intraoperative techniques for margin assessment in breast cancer surgery a meta-analysis. *Ann Surg*. 2017;265:300-310.
24. Olson TP, Harter J, Muñoz A, Mahvi DM, Breslin TM. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. *Ann Surg Oncol*. 2007;14:2953-2960.
25. Osako T, Nishimura R, Nishiyama Y, et al. Efficacy of intraoperative entire-circumferential frozen section analysis of lumpectomy margins during breast-conserving surgery for breast cancer. *Int J Clin Oncol*. 2015;20:1093-1101.
26. Kakiuchi Y, Choy B, Gordetsky J, et al. Role of frozen section analysis of surgical margins during robot-assisted laparoscopic radical prostatectomy: a 2608-case experience. *Hum Pathol*. 2013;44:1556-1562.

27. Nunez AL, Giannico GA, Mukhtar F, Dailey V, El-Galley R, Hameed O. Frozen section evaluation of margins in radical prostatectomy specimens: a contemporary study and literature review. *Ann Diagn Pathol*. 2016;24:11-18.
28. Duvdevani M, Laufer M, Kastin A, et al. Is frozen section analysis in nephron sparing surgery necessary? A clinicopathological study of 301 cases. *J Urol*. 2005;173:385-387.
29. DiNardo LJ, Lin J, Karageorge LS, Powers CN. Accuracy, utility, and cost of frozen section margins in head and neck cancer surgery. *Laryngoscope*. 2000;110:1773-1776.
30. Rosenthal EL, Warram JM, Bland KI, Zinn KR. The status of contemporary image-guided modalities in oncologic surgery. *Ann Surg*. 2015; 261:46-55.
31. De Boer E, Harlaar NJ, Taruttis A, et al. Optical innovations in surgery. *Br J Surg*. 2015;102:56-72.
32. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.
33. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529-536.
34. Hirst A, Philippou Y, Blazeby J, et al. No surgical innovation without evaluation: evolution and further development of the IDEAL framework and recommendations. *Ann Surg*. 2019;269:211-220.
35. Ha R, Friedlander LC, Hibshoosh H, et al. Optical coherence tomography: a novel imaging method for post-lumpectomy breast margin assessment—a multi-reader study. *Acad Radiol*. 2018;25: 279-287.
36. Erickson-Bhatt SJ, Nolan RM, Shemonski ND, et al. Real-time imaging of the resection bed using a handheld probe to reduce incidence of microscopic positive margins in cancer surgery. *Cancer Res*. 2015;75: 3706-3712.
37. Zysk AM, Chen K, Gabrielson E, et al. Intraoperative assessment of final margins with a handheld optical imaging probe during breast-conserving surgery may reduce the reoperation rate: results of a multicenter study. *Ann Surg Oncol*. 2015;22:3356-3362.
38. Butler-Henderson K, Lee AH, Price RI, Waring K. Intraoperative assessment of margins in breast conserving therapy: a systematic review. *Breast*. 2014;23:112-119.
39. Hekman MCH, Rijpkema M, Langenhuijsen JF, Boerman OC, Oosterwijk E, Mulders PFA. Intraoperative imaging techniques to support complete tumor resection in partial nephrectomy. *Eur Urol Focus*. 2018;4:960-968.
40. Kain JJ, Birkeland AC, Udayakumar N, et al. Surgical margins in oral cavity squamous cell carcinoma: current practices and future directions. *Laryngoscope*. 2020;130:128-138.
41. Tipirneni KE, Warram JM, Moore LS, et al. Oncologic procedures amenable to fluorescence-guided surgery. *Ann Surg*. 2017;266:36-47.
42. Snoeks TJA, Van Driel PBAA, Keereweer S, et al. Towards a successful clinical implementation of fluorescence-guided surgery. *Mol Imaging Biol*. 2014;16:147-151.
43. Zysk AM, Nguyen FT, Oldenburg AL, Marks DL, Boppart SA. Optical coherence tomography: a review of clinical development from bench to bedside. *J Biomed Opt*. 2007;12:051403.
44. Nijssen A, Koljenovic S, Bakker Schut TC, Caspers PJ, Puppels GJ. Towards oncological application of Raman spectroscopy. *J Biophotonics*. 2009;2:29-36.
45. Bigio IJ, Bown SG. Spectroscopic sensing of cancer and cancer therapy: current status of translational research. *Cancer Biol Ther*. 2004;3:259-267.
46. Akter S, Hossain MG, Nishidate I, Hazama H, Awazu K. Medical applications of reflectance spectroscopy in the diffusive and sub-diffusive regimes. *J Near Infrared Spectrosc*. 2018;26:337-350.
47. Balog J, Sasi-Szabo L, Kinross J, et al. Intraoperative tissue identification using rapid evaporative ionization mass spectrometry. *Sci Transl Med*. 2013;5:11.
48. van Keulen S, van den Berg NS, Nishio N, et al. Rapid, non-invasive fluorescence margin assessment: optical specimen mapping in oral squamous cell carcinoma. *Oral Oncol*. 2019;88:58-65.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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