



Intraoperative Margin Trials in Breast Cancer

Ava Armani¹ · Johanna Borst¹ · Sasha Douglas¹ · Nicole Goldharber¹ · Raeda Taj¹ · Sarah L. Blair¹

Accepted: 22 April 2022 / Published online: 26 May 2022

This is a U.S. government work and not under copyright protection in the U.S.; foreign copyright protection may apply 2022

Abstract

Purpose of Review Obtaining negative margins in breast conservation surgery continues to be a challenge. Re-excisions are difficult for patients and expensive for the health systems. This paper reviews the literature on current strategies and intraoperative clinical trials to reduce positive margin rates.

Recent Findings The best available data demonstrate that intraoperative imaging with ultrasound, intraoperative pathologic assessment such as frozen section, and cavity margins have been the most successful intraoperative strategies to reduce positive margins. Emerging technologies such as optical coherence tomography and fluorescent imaging need further study but may be important adjuncts.

Summary There are several proven strategies to reduce positive margin rates to < 10%. Surgeons should utilize best available resources within their institutions to produce the best outcomes for their patients.

Keywords Breast cancer surgical margins · Intraoperative imaging · Lumpectomy · Emerging technology · Optical coherence tomography · Fluorescence guided surgery

Introduction

Breast conservation surgery (BCS) has been the standard of care for early-stage breast cancer for over 20 years. When the original randomized controlled trials (RCTs) comparing BCS to mastectomy were performed, there was no survival difference between patients undergoing mastectomy compared to either BCS with no tumor on ink or BCS that did not assess margin status. However, the optimal width of the surgical margin to prevent in-breast recurrence has been debated given re-excision rates often exceeding 20% [1]. In 2013, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) guidelines defined the optimal margin width to be no tumor on ink for invasive cancers and 2 mm for ductal carcinoma in situ (DCIS) [2]. Subsequently, re-excision rates declined with a recent meta-analysis demonstrating a 35% decrease after the publication of these guidelines. Nevertheless, the literature still shows greater than

10% re-excision rates [3]. In this review, we will evaluate the literature on the standard and emerging methods for margin assessment to decrease the rate of positive margins.

Tumor Localization

There are a variety of tumor localization methods performed prior to surgery, especially to ensure identification of non-palpable tumors, that aim to achieve complete resection with adequate margins in BCS (Table 1). These include wire localization (WL), radioactive seed localization (RSL), and wireless devices.

Wire Localization

Wire localization has been the standard method of tumor localization for decades. First utilized in 1979, a wire with a hooked end was fashioned such that it could be inserted into the region of interest in the breast without dislodging. For localizing large areas of disease, multiple wires are placed to bracket the area of interest so that all the abnormal tissue within the boundaries of the wires can be surgically excised. The main disadvantage with wire localization is the need for placement within a short interval prior to surgery given that

This article is part of the Topical Collection on *Clinical Trials*

✉ Sarah L. Blair
sblair@health.ucsd.edu

¹ Department of Surgery, University of California San Diego, 3855 Health Science Dr, San Diego, La Jolla, CA 92093-0987, USA

Table 1 Summary of advantages and disadvantages of localization systems

	Inexpensive	No depth imitation	No minimal bracket spacing	Internal placement of device	Can be implanted several days before surgery	No radiation	Small size
Wire localization	X	X	X			X	
Radioactive seed localization		X		X	X		X
Radar				X	X	X	
Magnetic seeds				X	X	X	X
MOLLI				X	X	X	X
RFID tag				X	X	X	

the wire protrudes from the skin. This also results in risk of migration and discomfort for the patient.

Radioactive Seed

Beyond WL, there are a variety of wireless tumor localization techniques. Like wire localization, one device may be placed if a small area is to be removed, or multiple devices can be placed to bracket a large area of disease requiring excision. One such technique, RSL, was first proposed by Gray et al. in 2001 and involves the placement of a small titanium seed containing radioactive iodine-125 within the non-palpable tumor so that it can be identified using a handheld gamma detector [4]. Benefits of RSL over WL include a long half-life that allows for placement to occur days prior to surgery, making it more convenient for both the patient and the surgical team. Internal placement avoids extrusion of wire from the skin which mitigates risk of migration and improves patient experience [5, 6]. In the largest available randomized trial, RSL and WL did not significantly differ in positive margin rates. This trial had a low rate of positive margins in the WL group, and the RSL group had a significantly higher incidence of multifocal disease. No significant difference in positive margin rates was found for RSL (11%) and WL (12%, $p=0.99$), or for positive or close margins (RSL 19% and WL 22%; $p=0.61$). Mean operative time (min) was shorter for RSL (19 vs 22; $p<0.001$). Specimen volume, weight, reoperation, and localization times were similar [7]. Downsides of RSL compared to WL include a small amount of radiation exposure and inability to adjust improperly placed seeds [8].

Savi Scout Radar

More recently, a nonradioactive localization device called the Savi Scout Radar (Cianna Medical, Inc., Aliso Viejo, CA, USA) was FDA approved. This technique involves placement of a reflector within the breast mass that can be detected by a handheld radar-emitting device. Like RLS, the Savi Scout technology avoids the inconvenience and

discomforts associated with WL but has the advantage of also avoiding radiation exposure [9]. Patel and colleagues compared surgical outcomes of Scout localizations to WL in 42 matched patients and found no significant difference in median specimen volume, margin positivity rate, close margin rate, and re-excision rate [10]. A Savi Scout pilot study performed by Cox et al. observed similar re-excision rates as RSL (7%) and improved re-excision rates compared to WL (12–60%) [11]. The authors' subsequent multi-center, prospective study, however, demonstrated a slightly higher re-excision rate with Savi Scout (16.8%) than in the pilot study, yet still within acceptable limits as compared to WL [12]. A recent retrospective review of 512 patients reported 5.6% positive margins and 5.3% patients required re-excision with Savi Scout [13]. Therefore, overall, the Savi Scout localization system is equivalent in terms of margin outcomes to other localization methods.

One disadvantage of this system is that the reflector can be deactivated by electrocautery. Another potential disadvantage is signal interference when multiple Savi Scout reflectors are placed to bracket a lesion, although several studies have shown the feasibility of using multiple reflectors without technical difficulties.

MAGSEED

The MAGSEED (Endomagnetics, Cambridge, UK) is another FDA-approved nonradioactive non-wire device. Current knowledge about this magnetic marker is limited, but early clinical experience suggests that the MAGSEED device improved scheduling efficiency and patient comfort but is limited in depth of detection to 4 cm and cannot measure marker distance. Also, the signals from multiple seeds placed in close proximity (<2 cm) can be challenging to separate [14]. Magnetic seed marker deployment is also not advised in a patient who may undergo future breast MRI prior to surgery due to its void artifact of 4 to 6 cm distance, which influences the MRI diagnostic accuracy [15]. A retrospective study performed by Puneet reported a 9% positive

margins rate and 7.2% underwent a second procedure for margin re-excision [16].

MOLLI

The Magnetic Occult Lesion Localization Instrument (MOLLI Surgical Inc., Toronto, ON, Canada) is another wireless, nonradioactive alternative that was recently approved by the FDA. The system implants a small magnetic marker into the lesion to guide localization using a handheld probe [17]. The main benefit is it allows a depth of detection of up to 53 mm and can be used with metal instruments unlike other magnetic systems [18]. Twenty patients with non-palpable breast lesions at a single institution received a lumpectomy using the MOLLI guidance system. Negative margins were achieved in all cases with no patients requiring re-excision.

LOCalizer

Another promising technology is the LOCALizer™ (Hologic, Santa Clara, CA, USA) which is designed to mark breast lesions using a miniature radiofrequency identification (RFID) tag. Each tag has a unique identification number that is displayed on the reader and can be placed in the breast any time prior to or on the day of surgery. Limited data is available on this device, although small prospective trials have shown its efficacy [19]. The RFID tag produces artifact on MRI and thus may limit diagnostic accuracy of breast MRI when the RFID is in place. The FDA is not aware of any adverse events associated with RFID to date. The tags have a long history of use similar to those embedded in livestock and pets as a form of identification [20].

Two studies that compared LOCALizer™ with WL found that both modalities had comparable positive margin rates and rates of re-excision (15.6%).

Intraoperative Imaging

Besides procedures performed prior to surgery for tumor localization, intraoperative imaging is often used to help decrease positive margin and re-excision rates in BCS.

Intraoperative Ultrasound

Intraoperative US (IOUS) has several attractive advantages for localization and resection of the primary breast mass. These advantages include availability, portability, high safety profile, and real-time assessment of the target including depth from the closest skin surface [21]. Studies show IOUS can also be used to decrease positive margin rates in the setting of palpable breast masses. The COBALT trial

was a RCT comparing palpation guidance alone to palpation guidance with IOUS. The IOUS group not only required less additional treatments such as re-excision or radiotherapy boost but also achieved these results with smaller excision volumes [22]. A similar study conducted in 2019 corroborated these findings, again demonstrating superiority in achieving negative margins while avoiding excess tissue resection.

The benefit of IOUS has been less clear in the case of non-palpable breast lesions. When compared to WL, the current standard of care, the major benefit of IOUS is that it is performed in the operating room, thus avoiding the discomfort and inconvenience to the patient as well as the possible scheduling conflicts among departments associated with preoperative WL placement [23]. However, it is important to ensure that convenience does not supersede adequate resection. Several studies, including systematic reviews and meta-analyses, have demonstrated superiority or non-inferiority of IOUS over WL [24–26]. Of note, IOUS in such cases did not replace preoperative radiologic characterization of the tumor, which investigators acknowledge is still an essential part of perioperative planning. IOUS serves as an important adjunct to ensure appropriate resection. Recently, a RCT of 520 women with non-palpable breast cancer demonstrated that patients randomized to IOUS had significantly lower positive margins and re-excision rates [27]. Additionally, a recent single-institution study looked at the costs of IOUS with preoperative US visible clip (UVC) compared to WL and found that IOUS is the more cost-effective approach [28].

Specimen Radiography

While previous reviews have not found decreased reoperation rates for positive margins using specimen radiography (SR), the technique is still important in order to document the removal of calcifications (and to verify the removal of the tumor and/or localization devices) [23, 29–32]. Benefits of specimen radiography for margin assessment include relatively accessible and portable devices and, when compared to pathology, smaller economic impact and faster results (15–20 min) [29, 33]. However, the method has a more limited utility in patients with small lesions or high density breast tissue. Another important disadvantage is the “pancake phenomena” which describes the change in specimen shape when manipulated by the imaging machines [34].

Micro-computed Tomography

While SR provides 2 dimensional images, computed tomography (CT) has the advantage of providing 3 dimensional images. Some groups utilize micro-CT scanners which can be present in the operating room similar to SR. Several

studies show that micro-CT is a feasible tool for tumor evaluation during BCS that is relatively time efficient (< 30 min) [35–40]. However, these studies are limited by small sample size and only one study found a reduction in positive margin rates [39]. Otherwise, most agree that while 3D images are visually interesting, there were no significant advantages compared to SR. Other limitations of micro-CT included significant inter-observer variation and its use of gray scale which makes fibroglandular tissue difficult to distinguish from tumor. Given the novelty of the systems and therefore lack of consistent training, together with the small sample size in these studies, more research is needed to determine the utility of micro-CT for intraoperative margin assessment.

Optical Coherence Tomography

Optical imaging uses light and reflection of light (or optical scattering) to obtain detailed images based on tissue characteristics. This offers a minimally or virtually non-invasive method for intraoperative imaging and does not include the same radiation risks as X-ray or CT [41–49].

Optical coherence tomography (OCT) has been utilized for imaging in other specialties including ophthalmology, dermatology, and gastroenterology. Its potential use in breast surgery for intraoperative surgical margin assessment was first suggested by Boppart et al. who described OCT use in rat mammary tissue [42]. While multiple groups identified features that allowed them to distinguish between normal breast tissue, benign lesions, and malignant lesions, the tool is limited by penetration depth and the specific training required. Solutions for the limitation of penetration depth are being explored, including insertion of a needle probe and other handheld probes to display subsurface architecture [43, 49]. Zysk et al. conducted a multi-institution blinded study which included 46 patients undergoing BCT. OCT analysis was performed *ex vivo* on the cavity margins. For patients with a preoperative diagnosis of DCIS alone, positive margins were detected with 80% sensitivity and 69% specificity. It is a challenge to obtain negative margins in patients with DCIS because the disease can be more diffuse than shown by imaging, and guidelines recommend a 2 mm margin. While specialized training is required to interpret the OCT images, Ha et al. describe effective multidisciplinary training that takes an average of 3.4 h. Future larger studies will be needed to confirm its utility in reducing re-excision rates after BCS.

Marginprobe Device

The Marginprobe device, which is approved for use in the USA, utilizes radiofrequency spectroscopy and has been shown to be effective at assessing breast surgical margins intraoperatively. Marginprobe use was associated with

significant reductions in positive margin rates in one randomized trial (control arm rate of re-excision = 42%), and even lower in another (< 20%). Marginprobe specificity, however, has been reported less than 70% [50]. In the largest randomized trial using Marginprobe, use of the device more than tripled the rate of false-positive findings to > 50% of patients, resulting in a higher mean volume of resected tissue. Due to the high false-positive rate, Marginprobe may not be beneficial for routine use unless the rates of positive margins are exceedingly high. Given that re-excision rates have significantly decreased to < 20% nationally since the implementation of the SSO/ASTRO guidelines, the Marginprobe may be of less benefit [3].

ClearEdge

ClearEdge is a battery-powered, handheld device that can complete a full scan on resected tissue in less than 5 min using bioimpedance spectroscopy. A scan of the patient's normal breast tissue acts as a baseline for specific breast tissue features. This device has been studied in a two-phase trial [51]. The first phase validated the safety and accuracy of the imaging device when used *ex vivo* and the second phase assessed the reoperation rate when used intraoperatively. Results of this study demonstrated a sensitivity of 84.3% and 87.3% and a specificity of 81.9% and 75.6%. The re-excision rate in the second phase was 37%; however, had all images been interpreted appropriately and margins detected as abnormal re-excised, the adjusted rate of re-excision would have been 7%. While ClearEdge offers impressive speed and portability, its lack of sensitivity and specificity currently limits application in the clinical setting.

Pathology

Frozen Section Analysis

Like intraoperative imaging, intraoperative pathology can be used to decrease positive margin rates. Most surgeons do not use intraoperative frozen section analysis due to slow turnaround times (e.g., average increase of 30 min for frozen section), disruption to surgical workflow, interdepartmental logistical challenges, and resource requirements. Although there have been no RCTs performed on frozen section analysis, systematic review and meta-analyses have shown that this method is associated with a lower rate of reoperation for positive margins [52]. The most recent meta-analysis found pooled sensitivity was 0.86 (95% CI 0.78–0.91) and pooled specificity was 0.96 (95% CI 0.92–0.98) [53]. Because frozen section analysis involves added cost, its cost-effectiveness depends on the rate of positive margins and the subsequent need for re-excision without its use. Frozen section

analysis has been shown to be cost-effective for hospital and insurance payors when positive margin rates are > 25% [54]. Although it may decrease re-excision rates at the time of first surgery, it may not be of added value during subsequent surgeries for patients undergoing reoperation for positive margins [55].

Imprint Cytology

Another intraoperative technique utilized by a minority of surgeons is imprint cytology [52]. It is a technique where pathologist will imprint cells from the margins on slides. It requires expertise in cytology but is less labor intensive than frozen section. There are limited studies and no RCTs on the application of imprint cytology for real-time margin assessment. The most recent meta-analysis showed eleven studies reported on diagnostic accuracy data for imprint cytology. Pooled sensitivity was 0.91 (95% CI 0.71–0.97) and a pooled specificity of 0.95 (95% CI 0.90–0.98). Both meta-analyses suggested that imprint cytology and frozen section analysis are superior techniques in achieving negative excision margins when compared to no intraoperative pathologic assessment [53]. When appropriate expertise is available, imprint cytology can be considered for intraoperative margin management and appears to be at least as reliable as intraoperative frozen section analysis.

Cavity Margins

In addition to real-time intraoperative margin assessment, the excision of circumferential cavity margins may decrease positive margin rates. Chagpar et al. conducted a RCT to determine the effect of routine excision of circumferential cavity shave margins versus standard partial mastectomy, which included excision of selective margins, on outcomes after BCS [56]. 235 patients were randomized to each group. Surgeons were only made aware of which group each patient had been randomized to after first performing a partial mastectomy according to their usual practice. For those in the shave margins group, shave margins encompassing the entire cavity were removed. These included superior, inferior, medial, and lateral margins for all patients, and anterior and posterior margins in patients if the lumpectomy did not extend to the dermis and pectoralis fascia, respectively. The volume of shave margins was not standardized, and pathologists were blinded to the randomization. Patients assigned to the shave margins group initially had a positive margin rate of 36%, but more than half of these patients had the tumor cleared with additional cavity shaving, resulting in an overall positive margin rate of 19%, as compared to 34% in the standard partial

mastectomy group ($p = 0.01$). Within the standard partial mastectomy group, 27% had resection of selective margins based on surgeon discretion. There was a much lower re-excision rate in the shave margin groups as compared to the standard partial mastectomy group (10% versus 21%, $p = 0.02$). Importantly, despite a significantly larger volume of tissue excised in the shave margins group, there was no significant difference between the two groups in the patients' perception of cosmetic outcomes.

Several retrospective studies have shown similar findings. Hequet et al. showed that 25.3% of patients avoided re-excision for positive margins when additional shave margins were excised [57]. Corsi et al. found that 98.3% of patients in the shave margins group had negative margins as compared to 74.4% in the standard lumpectomy group ($p < 0.001$), with re-excision necessary in only 1.9% of patients in the shave margin groups versus 18.9% in the standard group ($p < 0.001$) [58]. Although shave margins increased operating time and pathological costs, reduced re-excisions mitigated this impact so that overall costs were similar between the two groups.

In another RCT, Chen et al. did not find a significant difference in positive margin rates with shave margins. 181 patients were randomized to either shave margins or standard partial mastectomy [59]. Similar to Chagpar et al., surgeons in this trial performed a partial mastectomy in their usual manner with additional selective margins prior to knowing the randomization group of each patient. Shave margins encompassed the entire excision cavity. However, results showed a 4.3% reduction in positive margin rates, which was not statistically significant. The authors suggested that smaller volumes of shave margins when compared to Chagpar et al. may have contributed to the differences in findings. Similarly, in a retrospective study, Vetter et al. found no statistical significance in positive margin or re-excision rates when comparing the shave margin group to the standard partial mastectomy group [60]. This may be due to the fact that an increased volume of tissue was not excised as compared to the standard BCS group.

Based on these studies, shave cavity margins can be considered to decrease positive margin rates if larger margins are taken, increasing the overall volume of tissue taken as compared to a standard partial mastectomy.

Emerging Technologies

Because current methods used to assess intraoperative margins are limited by cost, time, and personnel requirements, researchers are attempting to develop new diagnostic modalities to improve the speed, cost, reliability, and accuracy of these techniques.

Fluorescent Imaging

Fluorescent imaging probes including methylene blue (MB) and indocyanine green (ICG) have been used for decades for a variety of medical applications (Fig. 1). Recently, these probes have been gaining momentum as a method for assessing tumor margins intraoperatively with multiple progressing onto clinical trials (Table 2) [66]. Lui et al. found that using fluorescent guidance with ICG, a probe that rapidly

binds to plasma proteins, yields a 100% positive predictive value for lesions with no false-positive localization and 94.6% satisfactory margins [67]. Similarly, Kedrzycki et al. demonstrated impressive diagnostic accuracy using an ICG fluorescent probe [68]. By administering 0.25 mg/kg of ICG 25 min prior to tumor excision, researchers were able to achieve a tumor detection sensitivity and specificity of 0.82 and 0.93, respectively. MB, another non-targeted dye, has also been studied as a marker for detecting intraoperative

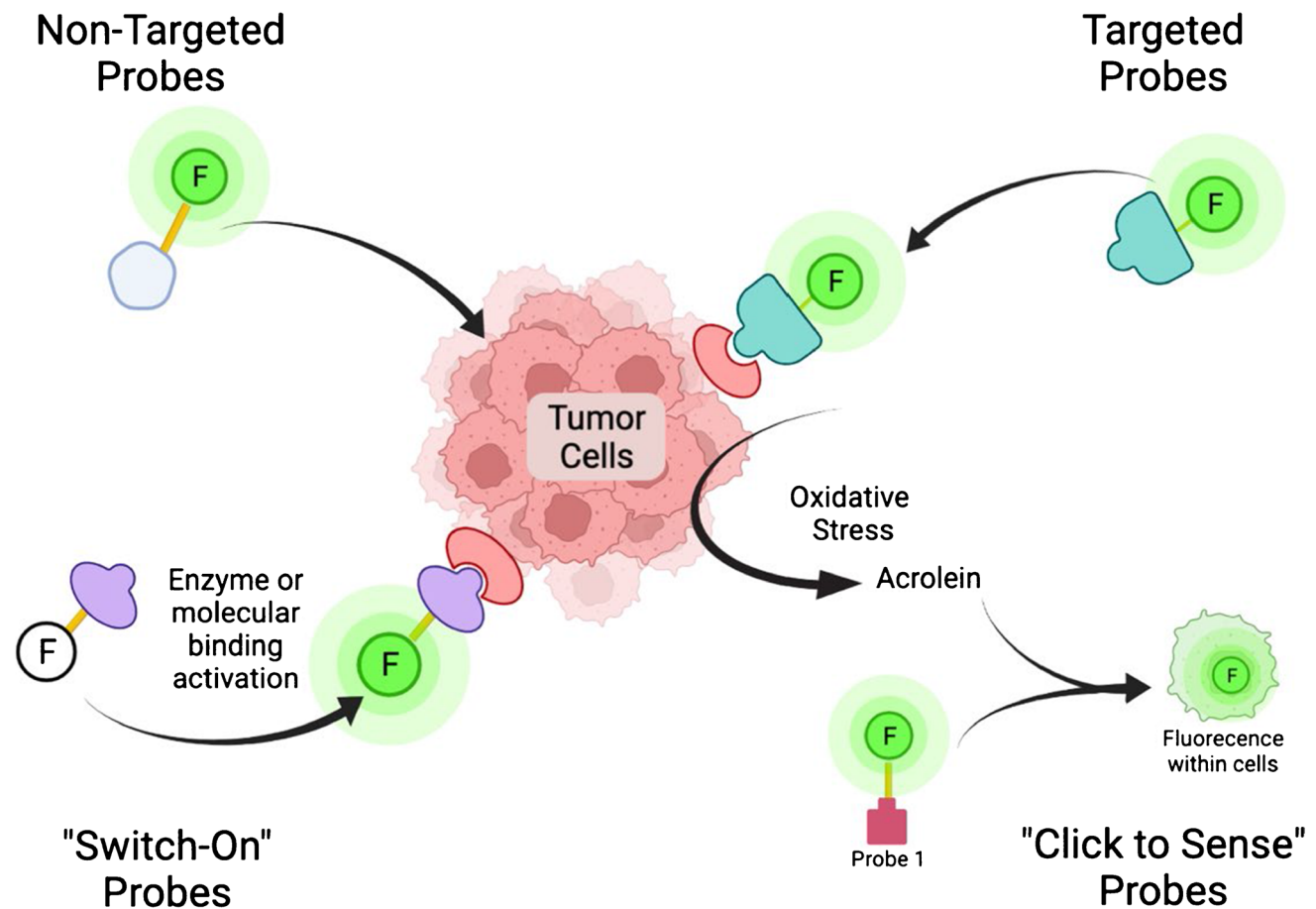


Fig. 1 Categories of fluorescent imaging probes

Table 2 Clinical trials assessing fluorescent imaging in breast cancer surgery

Agent	Target/activating protease	Imaging system	Patients	Trial type	References
LUM015	Cathepsin	LUM imaging system	15	Phase 1	Whitley et al. [61]
Bevacizumab-IRDye800CW	VEGF-A	TUM optical imaging system	20	Phase 1	Lamberts et al. [62]
AVB-620	Matrix metalloproteinases	Avelas imaging system	27	Phase 1	Unkart et al. [63]
5-ALA	Intra-cellular heme biosynthesis	PRODIGI	54	Phase 2	Ottolino-Perry et al. [64]
ICG-F	Non-targeted	Ultrasound	414	Phase 2	Lee et al. [65]

5-ALA, 5-aminolevulinic acid hydrochloride; ICG-F, indocyanine green fluorescence; TUM, Technical University Munich; VEGF-A, vascular endothelial growth factor A

tumor margins. Zhang et al. reported a sensitivity and positive predictive value of 0.63 and 0.79 respectively after injection of 1 mg/kg of MB 3 h prior to surgery [69]. However, concern has been raised that the uptake of MB in older patients or patients who have previously received chemotherapy may not be sufficient to reliably identify positive tumor margins [70].

ICG and MB take advantage of generalized properties of cancers, but ideally, the fluorescent agent would accumulate exclusively in or around tumor tissue, providing excellent contrast between the tumor or affected lymph node and healthy tissue. Such a probe would exhibit high selectivity for tumors with high tumor to background ratios. To achieve this, researchers are working to develop probes that target tumor-specific antigens and are attempting to utilize fluorescent agents that capitalize on tumor-specific enzymatic activation. Bevacizumab-800CW is a fluorescent probe based on monoclonal antibodies targeting vascular endothelial growth factor (VEGF) that has progressed into clinical testing [71]. Other targeted dyes include EC17 which binds to the Folate receptor alpha and Tozuleristide, which binds to matrix metalloproteinases and AnnexinA2 [72, 73]. To further enhance tumor margin detection, researchers have designed more advanced probes that do not emit a signal until engaging with their unique target. The Lumicell system uses LUM015, a protease-activated fluorescent probe that exists in a fluorescently inert, quenched state until it reacts with cathepsin secreted by breast cancer cells [71]. Other “switch on” probes currently being studied are target matrix metalloproteinase, beta-galactosidase, and γ -glutamyltransferase enzymes, all of which are upregulated by tumor cells. Another targeted probe under development detects the presence of acrolein, a biomarker associated with oxidative stress that is overproduced by most cancer cells. This method exhibits fluorescence that is proportional to the acrolein concentration generated by the cells and enables the visualization of cancer morphology allowing discrimination between subtypes of tumors [74]. While promising, the clinical utility of many of these probes is currently limited due to cost and issues surrounding their timing of administration.

Deep Learning and Artificial Intelligence

Efforts to incorporate automatic deep learning and artificial intelligence algorithms have also been made to increase the efficiency and reliability of intraoperative tumor margin detection and reduce the reliance on well-trained pathologists. The CAMELYON16 international competition showed the effectiveness of automated deep learning algorithms in diagnosing the H&E sections of axillary lymph node metastasis [75]. The best algorithms performed comparably to

pathologists without time constraints and significantly better than pathologists when there was a time constraint, a more realistic representation of standard workflow. There are additional reports that show the feasibility of combining new imaging technology with algorithms to interpret information for margin assessment, but larger validation datasets are necessary to demonstrate efficacy [76]. The incorporation of emerging artificial intelligence algorithms has promise, with studies indicating their clinical feasibility and supporting future exploration.

Conclusion

BCS is the standard of care for early-stage breast cancer, and re-excision is recommended for positive margins for invasive breast cancer and less than 2 mm margins for DCIS based on current guidelines. Re-excision rates vary widely in the literature and are not affected by type of localization device. Intraoperative modalities that have been shown to reduce positive margins with high quality data include IOUS, intraoperative pathologic margin assessment [of any type other than margin devices], and routine planned shave cavity margins. These findings are consistent with prior RCTs, meta-analyses, and observational studies. None of these methods is standard of care, but rather the selection of which to adopt depends on patient factors, surgeon setting, resource availability, and facility-specific barriers. If re-excision rates are not at or below target goals with current practices, then adopting new processes may add value. Emerging technologies such as OCT, micro-CT, and fluorescent guided surgery are exciting but further data is needed to assess their benefit.

Declarations

Conflict of Interest Sarah Blair MD’s husband owns stock in Viewpoint Medical.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- McCahill LE, Single RM, Aiello Bowles EJ, et al. Variability in reexcision following breast conservation surgery. *JAMA*. 2012;307(5):467–75. <https://doi.org/10.1001/jama.2012.43> [publishedOnlineFirst:2012/02/03].
- 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. *Int J Radiat Oncol Biol Phys*. 2014;88(3):553–64. <https://doi.org/10.1016/j.ijrobp.2013.11.012>.
- Havel L, Naik H, Ramirez L, et al. Impact of the SSO-ASTRO margin guideline on rates of re-excision after lumpectomy for breast cancer: a meta-analysis. *Ann Surg Oncol*. 2019;26(5):1238–44. <https://doi.org/10.1245/s10434-019-07247-5> [publishedOnlineFirst:2019/02/23].
- Gray RJ, Salud C, Nguyen K, et al. Randomized prospective evaluation of a novel technique for biopsy or lumpectomy of nonpalpable breast lesions: radioactive seed versus wire localization. *Ann Surg Oncol*. 2001;8(9):711–5. <https://doi.org/10.1007/s10434-001-0711-3> [publishedOnlineFirst:2001/10/13].
- Wang GL, Tsikouras P, Zuo HQ, et al. Radioactive seed localization and wire guided localization in breast cancer: a systematic review and meta-analysis. *J BUON*. 2019;24(1):48–60. [published Online First: 2019/04/04].
- Da Silva M, Porembka J, Mokdad AA, et al. Bracketed radioactive seed localization vs bracketed wire-localization in breast surgery. *Breast J*. 2018;24(2):161–6. <https://doi.org/10.1111/tbj.12854> [publishedOnlineFirst:2017/07/15].
- Lovrics PJ, Goldsmith CH, Hodgson N, et al. A multicentered, randomized, controlled trial comparing radioguided seed localization to standard wire localization for nonpalpable, invasive and in situ breast carcinomas. *Ann Surg Oncol*. 2011;18(12):3407–14. <https://doi.org/10.1245/s10434-011-1699-y> [publishedOnlineFirst:2011/05/03].
- Goudreau SH, Joseph JP, Seiler SJ. Preoperative radioactive seed localization for nonpalpable breast lesions: technique, pitfalls, and solutions. *Radiographics*. 2015;35(5):1319–34. <https://doi.org/10.1148/rg.2015140293> [publishedOnlineFirst:2015/08/15].
- Srouf MK, Kim S, Amers F, et al. Comparison of multiple wire, radioactive seed, and Savi Scout. *Ann Surg Oncol*. 2021;28(4):2212–8. <https://doi.org/10.1245/s10434-020-09159-1> [publishedOnlineFirst:20200928].
- Patel SN, Mango VL, Jadeja P, et al. Reflector-guided breast tumor localization versus wire localization for lumpectomies: a comparison of surgical outcomes. *Clin Imaging*. 2018;47:14–7. <https://doi.org/10.1016/j.clinimag.2017.07.020> [publishedOnlineFirst:2017/08/19].
- Cox CE, Garcia-Henriquez N, Glancy MJ, et al. Pilot study of a new nonradioactive surgical guidance technology for locating nonpalpable breast lesions. *Ann Surg Oncol*. 2016;23(6):1824–30. <https://doi.org/10.1245/s10434-015-5079-x> [publishedOnlineFirst:2016/02/06].
- Cox CE, Russell S, Prowler V, et al. A prospective, single arm, multi-site, clinical evaluation of a nonradioactive surgical guidance technology for the location of nonpalpable breast lesions during excision. *Ann Surg Oncol*. 2016;23(10):3168–74. <https://doi.org/10.1245/s10434-016-5405-y> [publishedOnlineFirst:2016/07/30].
- Tingen JS, McKinley BP, Rinkliff JM, et al. Savi Scout Radar localization versus wire localization for breast biopsy regarding positive margin, complication, and reoperation rates. *Am Surg*. 2020;86(8):1029–31. <https://doi.org/10.1177/0003134820939903> [publishedOnlineFirst:2020/07/30].
- Pieszko K, Wichtowski M, Cieciorowski M, et al. Evaluation of the nonradioactive inducible magnetic seed system Magseed for preoperative localization of nonpalpable breast lesions—initial clinical experience. *Contemp Oncol (Pozn)*. 2020;24(1):51–4. <https://doi.org/10.5114/wo.2020.93677> [publishedOnlineFirst:2020/06/10].
- Fung WY, Wong T, Chau CM, et al. Safety and efficacy of magnetic seed localisation of non-palpable breast lesions: pilot study in a Chinese population. *Hong Kong Med J*. 2020;26(6):500–9. <https://doi.org/10.12809/hkmj208559> [publishedOnlineFirst:2020/12/12].
- Singh P, Scoggins ME, Sahin AA, et al. Effectiveness and safety of Magseed-localization for excision of breast lesions: a prospective, phase IV trial. *Ann Surg Open*. 2020;1(2). <https://doi.org/10.1097/as9.000000000000008>
- Look Hong N, Wright FC, Semple M, et al. Results of a phase I, non-randomized study evaluating a Magnetic Occult Lesion Localization Instrument (MOLLI) for excision of non-palpable breast lesions. *Breast Cancer Res Treat*. 2020;179(3):671–6. <https://doi.org/10.1007/s10549-019-05499-z> [publishedOnlineFirst:2019/11/23].
- Nicolae A, Dillon J, Semple M, et al. Evaluation of a ferromagnetic marker technology for intraoperative localization of nonpalpable breast lesions. *AJR Am J Roentgenol*. 2019;212(4):727–33. <https://doi.org/10.2214/AJR.18.20195> [publishedOnlineFirst:2019/01/24].
- Dauphine C, Reicher JJ, Reicher MA, et al. A prospective clinical study to evaluate the safety and performance of wireless localization of nonpalpable breast lesions using radiofrequency identification technology. *AJR Am J Roentgenol*. 2015;204(6):W720–3. <https://doi.org/10.2214/AJR.14.13201> [publishedOnlineFirst:2015/05/23].
- Malter W, Holtschmidt J, Thangarajah F, et al. First reported use of the Faxitron LOCALIZER™ radiofrequency identification (RFID) system in Europe—a feasibility trial, surgical guide and review for non-palpable breast lesions. *In Vivo*. 2019;33(5):1559–64. <https://doi.org/10.21873/invivo.11637>.
- Dogan BE, Whitman GJ. Intraoperative breast ultrasound. *Semin Roentgenol*. 2011;46(4):280–4. <https://doi.org/10.1053/j.ro.2011.02.009> [publishedOnlineFirst:2011/11/01].
- Krekel NM, Haloua MH, Lopes Cardozo AM, et al. Intraoperative ultrasound guidance for palpable breast cancer excision (COBALT trial): a multicentre, randomised controlled trial. *Lancet Oncol*. 2013;14(1):48–54. [https://doi.org/10.1016/S1470-2045\(12\)70527-2](https://doi.org/10.1016/S1470-2045(12)70527-2) [publishedOnlineFirst:2012/12/12].
- Gray RJ, Pockaj BA, Garvey E, et al. Intraoperative margin management in breast-conserving surgery: a systematic review of the literature. *Ann Surg Oncol*. 2018;25(1):18–27. <https://doi.org/10.1245/s10434-016-5756-4> [publishedOnlineFirst:2017/01/07].
- Eggemann H, Costa SD, Ignatov A. Ultrasound-guided versus wire-guided breast-conserving surgery for nonpalpable breast cancer. *Clin Breast Cancer*. 2016;16(1):e1–6. <https://doi.org/10.1016/j.clbc.2015.09.001> [publishedOnlineFirst:2015/10/07].
- Ahmed M, Douek M. Intra-operative ultrasound versus wire-guided localization in the surgical management of non-palpable breast cancers: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;140(3):435–46. <https://doi.org/10.1007/s10549-013-2639-2> [publishedOnlineFirst:2013/07/24].
- Ramos M, Diaz JC, Ramos T, et al. Ultrasound-guided excision combined with intraoperative assessment of gross macroscopic margins decreases the rate of reoperations for non-palpable invasive breast cancer. *Breast*. 2013;22(4):520–4. <https://doi.org/10.1016/j.breast.2012.10.006> [publishedOnlineFirst:2012/11/01].
- Hu X, Li S, Jiang Y, et al. Intraoperative ultrasound-guided lumpectomy versus wire-guided excision for nonpalpable breast cancer.

- J Int Med Res. 2020;48(1):300060519896707. <https://doi.org/10.1177/0300060519896707> [publishedOnlineFirst:2020/01/16].
28. Konen J, Murphy S, Berkman A, et al. Intraoperative ultrasound guidance with an ultrasound-visible clip: a practical and cost-effective option for breast cancer localization. *J Ultrasound Med.* 2020;39(5):911–7. <https://doi.org/10.1002/jum.15172> [publishedOnlineFirst:2019/11/19].
 29. Chan BK, Wiseberg-Firtell JA, Jois RH, et al. Localization techniques for guided surgical excision of non-palpable breast lesions. *Cochrane Database Syst Rev.* 2015(12):CD009206. <https://doi.org/10.1002/14651858.CD009206.pub2> [published Online First: 2016/01/01].
 30. Versteegden DPA, Keizer LGG, Schlooz-Vries MS, et al. Performance characteristics of specimen radiography for margin assessment for ductal carcinoma in situ: a systematic review. *Breast Cancer Res Treat.* 2017;166(3):669–79. <https://doi.org/10.1007/s10549-017-4475-2> [publishedOnlineFirst:2017/08/24].
 31. Lange M, Reimer T, Hartmann S, et al. The role of specimen radiography in breast-conserving therapy of ductal carcinoma in situ. *Breast.* 2016;26:73–9. <https://doi.org/10.1016/j.breast.2015.12.014> [publishedOnlineFirst:20160201].
 32. van Riet PA, Giorgio Arcidiacono P, Petrone M, et al. Combined versus single use 20 G fine-needle biopsy and 25 G fine-needle aspiration for endoscopic ultrasound-guided tissue sampling of solid gastrointestinal lesions. *Endoscopy.* 2020;52(1):37–44. <https://doi.org/10.1055/a-0966-8755> [publishedOnlineFirst:20190722].
 33. Ihrai T, Quaranta D, Fouche Y, et al. Intraoperative radiological margin assessment in breast-conserving surgery. *Eur J Surg Oncol.* 2014;40(4):449–53. <https://doi.org/10.1016/j.ejso.2014.01.002> [publishedOnlineFirst:2014/01/29].
 34. van Riet YE, Schipper RJ, van Merriënboer F, et al. Is specimen radiography still necessary in patients with non-palpable breast cancer undergoing breast-conserving surgery using radioactive I-125 seed localization? *Clin Imaging.* 2021;69:311–7. <https://doi.org/10.1016/j.clinimag.2020.10.004> [publishedOnlineFirst:2020/10/13].
 35. Abel TN, Bourke AG. Can micro-computed tomography imaging improve interpretation of macroscopic margin assessment of specimen radiography in excised breast specimens? *J Cancer Res Ther.* 2020;16(6):1366–70. https://doi.org/10.4103/jcrt.JCRT_949_19 [publishedOnlineFirst:2020/12/22].
 36. DiCorpo D, Tiwari A, Tang R, et al. The role of micro-CT in imaging breast cancer specimens. *Breast Cancer Res Treat.* 2020;180(2):343–57. <https://doi.org/10.1007/s10549-020-05547-z> [publishedOnlineFirst:2020/02/06].
 37. Janssen NNY, van Seijen M, Loo CE, et al. Feasibility of micro-computed tomography imaging for direct assessment of surgical resection margins during breast-conserving surgery. *J Surg Res.* 2019;241:160–9. <https://doi.org/10.1016/j.jss.2019.03.029> [publishedOnlineFirst:20190423].
 38. McClatchy DM, Zuurbier RA, Wells WA, et al. Micro-computed tomography enables rapid surgical margin assessment during breast conserving surgery (BCS): correlation of whole BCS micro-CT readings to final histopathology. *Breast Cancer Res Treat.* 2018;172(3):587–95. <https://doi.org/10.1007/s10549-018-4951-3> [publishedOnlineFirst:20180917].
 39. Qiu SQ, Dorrius MD, de Jongh SJ, et al. Micro-computed tomography (micro-CT) for intraoperative surgical margin assessment of breast cancer: a feasibility study in breast conserving surgery. *Eur J Surg Oncol.* 2018;44(11):1708–13. <https://doi.org/10.1016/j.ejso.2018.06.022> [publishedOnlineFirst:2018/07/15].
 40. Tang R, Saksena M, Coopey SB, et al. Intraoperative micro-computed tomography (micro-CT): a novel method for determination of primary tumour dimensions in breast cancer specimens. *Br J Radiol.* 2016;89(1058):20150581. <https://doi.org/10.1259/bjr.20150581> [publishedOnlineFirst:2015/11/17].
 41. Assayag O, Antoine M, Sigal-Zafrani B, et al. Large field, high resolution full-field optical coherence tomography: a pre-clinical study of human breast tissue and cancer assessment. *Technol Cancer Res Treat.* 2014;13(5):455–68. <https://doi.org/10.7785/tcrte.xpress.2013.600254> [publishedOnlineFirst:20130831].
 42. Boppart SA, Luo W, Marks DL, et al. Optical coherence tomography: feasibility for basic research and image-guided surgery of breast cancer. *Breast Cancer Res Treat.* 2004;84(2):85–97. <https://doi.org/10.1023/B:BREA.0000018401.13609.54>.
 43. Curatolo A, McLaughlin RA, Quirk BC, et al. Ultrasound-guided optical coherence tomography needle probe for the assessment of breast cancer tumor margins. *AJR Am J Roentgenol.* 2012;199(4):W520–2. <https://doi.org/10.2214/AJR.11.7284>.
 44. 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(3):279–87. <https://doi.org/10.1016/j.acra.2017.09.018> [publishedOnlineFirst:20171123].
 45. Hsiung PL, Phatak DR, Chen Y, et al. Benign and malignant lesions in the human breast depicted with ultrahigh resolution and three-dimensional optical coherence tomography. *Radiology.* 2007;244(3):865–74. <https://doi.org/10.1148/radiol.2443061536> [publishedOnlineFirst:20070713].
 46. Nguyen FT, Zysk AM, Chaney EJ, et al. Intraoperative evaluation of breast tumor margins with optical coherence tomography. *Cancer Res.* 2009;69(22):8790–6. <https://doi.org/10.1158/0008-5472.CAN-08-4340>.
 47. Schmidt H, Connolly C, Jaffer S, et al. Evaluation of surgically excised breast tissue microstructure using wide-field optical coherence tomography. *Breast J.* 2020;26(5):917–23. <https://doi.org/10.1111/tbj.13663> [publishedOnlineFirst:20191014].
 48. Zhou C, Cohen DW, Wang Y, et al. Integrated optical coherence tomography and microscopy for ex vivo multiscale evaluation of human breast tissues. *Cancer Res.* 2010;70(24):10071–9. <https://doi.org/10.1158/0008-5472.CAN-10-2968> [publishedOnlineFirst:20101105].
 49. 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(10):3356–62. <https://doi.org/10.1245/s10434-015-4665-2> [publishedOnlineFirst:20150723].
 50. Karni T, Pappo I, Sandbank J, et al. A device for real-time, intraoperative margin assessment in breast-conservation surgery. *Am J Surg.* 2007;194(4):467–73. <https://doi.org/10.1016/j.amjsurg.2007.06.013>.
 51. Dixon JM, Renshaw L, Young O, et al. Intra-operative assessment of excised breast tumour margins using ClearEdge imaging device. *Eur J Surg Oncol.* 2016;42(12):1834–40. <https://doi.org/10.1016/j.ejso.2016.07.141> [publishedOnlineFirst:20160810].
 52. Blair SL, Thompson K, Rococco J, et al. Attaining negative margins in breast-conservation operations: is there a consensus among breast surgeons? *J Am Coll Surg.* 2009;209(5):608–13. <https://doi.org/10.1016/j.jamcollsurg.2009.07.026> [publishedOnlineFirst:20090911].
 53. 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(2):300–10. <https://doi.org/10.1097/SLA.0000000000001897>.
 54. Osborn JB, Keeney GL, Jakub JW, et al. Cost-effectiveness analysis of routine frozen-section analysis of breast margins compared with reoperation for positive margins. *Ann Surg Oncol.*

- 2011;18(11):3204–9. <https://doi.org/10.1245/s10434-011-1956-0> [publishedOnlineFirst:20110823].
55. Jorns JM, Daignault S, Sabel MS, et al. Is intraoperative frozen section analysis of reexcision specimens of value in preventing reoperation in breast-conserving therapy? *Am J Clin Pathol.* 2014;142(5):601–8. <https://doi.org/10.1309/AJCPRSOA2G8RLEXY>.
 56. Chagpar AB, Killelea BK, Tsangaris TN, et al. A randomized, controlled trial of cavity shave margins in breast cancer. *N Engl J Med.* 2015;373(6):503–10. <https://doi.org/10.1056/NEJMoa1504473> [publishedOnlineFirst:20150530].
 57. Héquet D, Bricou A, Delpéch Y, et al. Surgical management modifications following systematic additional shaving of cavity margins in breast-conservation treatment. *Ann Surg Oncol.* 2011;18(1):114–8. <https://doi.org/10.1245/s10434-010-1211-0> [publishedOnlineFirst:20100714].
 58. Corsi F, Sorrentino L, Bonzini M, et al. Cavity shaving reduces involved margins and reinterventions without increasing costs in breast-conserving surgery: a propensity score-matched study. *Ann Surg Oncol.* 2017;24(6):1516–24. <https://doi.org/10.1245/s10434-017-5774-x> [publishedOnlineFirst:20170123].
 59. Chen K, Zhu L, Chen L, et al. Circumferential shaving of the cavity in breast-conserving surgery: a randomized controlled trial. *Ann Surg Oncol.* 2019;26(13):4256–63. <https://doi.org/10.1245/s10434-019-07725-w> [publishedOnlineFirst:2019]0819].
 60. Vetter C, Ashok A, Perez M, et al. Impact of systematic cavity shave margins in breast-conserving surgery at a large community hospital with a low baseline re-excision rate. *Breast J.* 2020;26(10):1960–5. <https://doi.org/10.1111/tbj.14057> [publishedOnlineFirst:20201019].
 61. Whitley MJ, Cardona DM, Lazarides AL, et al. A mouse-human phase I co-clinical trial of a protease-activated fluorescent probe for imaging cancer. *Sci Transl Med* 2016;8(320):320ra4. <https://doi.org/10.1126/scitranslmed.aad0293>
 62. Lamberts LE, Koch M, de Jong JS, et al. Tumor-specific uptake of fluorescent bevacizumab-IRDye800CW microdosing in patients with primary breast cancer: a phase I feasibility study. *Clin Cancer Res.* 2017;23(11):2730–41. <https://doi.org/10.1158/1078-0432.CCR-16-0437> [publishedOnlineFirst:20161109].
 63. Unkart JT, Chen SL, Wapnir IL, et al. Intraoperative tumor detection using a ratiometric activatable fluorescent peptide: a first-in-human phase I study. *Ann Surg Oncol.* 2017;24(11):3167–73. <https://doi.org/10.1245/s10434-017-5991-3> [publishedOnlineFirst:20170711].
 64. Ottolino-Perry K, Shahid A, DeLuca S, et al. Intraoperative fluorescence imaging with aminolevulinic acid detects grossly occult breast cancer: a phase II randomized controlled trial. *Breast Cancer Res.* 2021;23(1):72. <https://doi.org/10.1186/s13058-021-01442-7> [publishedOnlineFirst:20210712].
 65. Lee EG, Kim SK, Han JH, et al. Surgical outcomes of localization using indocyanine green fluorescence in breast conserving surgery: a prospective study. *Sci Rep.* 2021;11(1):9997. <https://doi.org/10.1038/s41598-021-89423-w> [publishedOnlineFirst:20210511].
 66. Nagaya T, Nakamura YA, Choyke PL, et al. Fluorescence-guided surgery. *Front. Oncol.* 2017;7:314. <https://doi.org/10.3389/fonc.2017.00314> [publishedOnlineFirst:20171222].
 67. Liu J, Guo W, Tong M. Intraoperative indocyanine green fluorescence guidance for excision of nonpalpable breast cancer. *World J Surg Oncol.* 2016;14(1):266. <https://doi.org/10.1186/s12957-016-1014-2> [publishedOnlineFirst:20161018].
 68. Kedrzycki MS, Leiloglou M, Chalau V, et al. The impact of temporal variation in indocyanine green administration on tumor identification during fluorescence guided breast surgery. *Ann Surg Oncol.* 2021;28(10):5617–25. <https://doi.org/10.1245/s10434-021-10503-2> [publishedOnlineFirst:20210804].
 69. Zhang C, Jiang D, Huang B, et al. Methylene blue-based near-infrared fluorescence imaging for breast cancer visualization in resected human tissues. *Technol Cancer Res Treat.* 2019;18:1533033819894331. <https://doi.org/10.1177/1533033819894331>.
 70. Balasundaram G, Krafft C, Zhang R, et al. Biophotonic technologies for assessment of breast tumor surgical margins—a review. *J Biophotonics.* 2021;14(1): e202000280. <https://doi.org/10.1002/jbio.202000280> [publishedOnlineFirst:20201012].
 71. Pradipta AR, Tanei T, Morimoto K, et al. Emerging technologies for real-time intraoperative margin assessment in future breast-conserving surgery. *Adv Sci (Weinh).* 2020;7(9):1901519. <https://doi.org/10.1002/advs.201901519> [publishedOnlineFirst:20200317].
 72. Tummers QR, Hoogstins CE, Gaarenstroom KN, et al. Intraoperative imaging of folate receptor alpha positive ovarian and breast cancer using the tumor specific agent EC17. *Oncotarget.* 2016;7(22):32144–55. <https://doi.org/10.18632/oncotarget.8282>.
 73. Dintzis SM, Hansen S, Harrington KM, et al. Real-time visualization of breast carcinoma in pathology specimens from patients receiving fluorescent tumor-marking agent tozuleristide. *Arch Pathol Lab Med.* 2019;143(9):1076–83. <https://doi.org/10.5858/arpa.2018-0197-OA> [publishedOnlineFirst:20181214].
 74. Tanei T, Pradipta AR, Morimoto K, et al. Cascade reaction in human live tissue allows clinically applicable diagnosis of breast cancer morphology. *Adv Sci (Weinh).* 2019;6(2):1801479. <https://doi.org/10.1002/advs.201801479> [publishedOnlineFirst:20181127].
 75. Ehteshami Bejnordi B, Veta M, Johannes van Diest P, et al. Diagnostic assessment of deep learning algorithms for detection of lymph node metastases in women with breast cancer. *JAMA.* 2017;318(22):2199–210. <https://doi.org/10.1001/jama.2017.14585>
 76. Singla N, Dubey K, Srivastava V. Automated assessment of breast cancer margin in optical coherence tomography images via pretrained convolutional neural network. *J Biophotonics.* 2019;12(3): e201800255. <https://doi.org/10.1002/jbio.201800255> [publishedOnlineFirst:20181113].

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.