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Handheld Radiofrequency Spectroscopy for Intraoperative Assessment of Surgical Margins During Breast-Conserving Surgery

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Related Policies (if applicable)
None

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Coverage

Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

As part of the treatment of localized breast cancer, breast-conserving surgery is optimally achieved by attaining tumor-free margins around the surgical resection site. (1) Failure to

achieve clear margins will often require additional surgery to re-excise breast tissue. Currently, histologic examination of excised tissues after completion of surgery is the only method to determine definitively whether clear margins were achieved. Intraoperative methods of assessing surgical margins, such as specimen imaging, frozen section pathology, and touch print cytology, are either not highly accurate, not commonly available, or require considerable time and resources.

A device to detect positive margins should have a high sensitivity, indicating the ability to accurately detect any tumor found in the margins, ideally above 95%. While specificity is less important, excess false-positive margin detection would lead to additional unnecessary tissue removal. A new device should have a specificity at least matching current standard best practices, estimated at 85%. (2)

The MarginProbe is an intraoperative device which uses radiofrequency spectroscopy to measure the dielectric properties of tissue into which it comes in contact. Cancer cells and normal breast tissues produce different signals. A handheld probe is applied to a small area of the lumpectomy specimen and analyzes whether the tissue is likely malignant or benign. The device gives a positive or negative reading for each touch. If any touch on a particular margin gives a positive reading, the margin is considered to be positive and more tissue should be re-excised if possible. The device can only be used on the main lumpectomy specimen; it cannot be used on shavings or in the lumpectomy cavity of the patient's breast. Use of MarginProbe is intended to increase the probability that the surgeon will achieve clear margins in the initial surgery, thus avoiding the need for a second procedure to excise more breast tissue.

Regulatory Status

In December 2012, MarginProbe® (Dune Medical Devices, Caesarea, Israel) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤1 mm) of the main ex vivo lumpectomy specimen after primary excision (P110014). It is indicated for intraoperative use in conjunction with standard methods (e.g., intraoperative imaging and palpation) for patients undergoing lumpectomy for previously diagnosed breast cancer. FDA product code: OEE.

Rationale

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Medical policies assess the evidence on whether a test is clinically valid and clinically useful.

Technical reliability is outside the scope of these policies, and credible information on technical reliability is available from other sources.

Handheld Radiofrequency for Breast Cancer Margin Detection

Clinical Context and Test Purpose

Breast cancer outcomes can be optimized by a thorough excision of breast cancer. A standard surgical practice of surgeons is to remove more breast tissue if pathologic examination of the initial excision shows positive margins. Handheld radiofrequency spectroscopy (e.g., MarginProbe) evaluates the resected specimen to determine if further excision is necessary during the initial lumpectomy. The use of handheld radiofrequency spectroscopy should reduce re-excision rates, maintain low cancer recurrence rates, and minimize the volume of breast tissue excised.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with localized breast cancer or ductal carcinoma in situ (DCIS) who are undergoing lumpectomy.

Interventions

The technology being considered is handheld radiofrequency spectroscopy (e.g., MarginProbe) as an adjunct to standard assessment of margins.

Comparators

The following practice is currently being used: standard intraoperative assessment of margins such as inspection, palpation, intraoperative imaging, and intraoperative histologic examination. The technique used can vary by institution and surgeon. The incremental benefit of handheld radiofrequency spectroscopy (e.g., MarginProbe) may vary according to what is considered the standard intraoperative assessment.

Outcomes

The short-term outcome of interest is the re-excision rate. However, the re-excision rate can only be considered a valid outcome if long-term outcomes (e.g., local recurrence rate, long-term cancer outcome) are either equivalent or in favor of handheld radiofrequency spectroscopy (e.g., MarginProbe). For example, if the use of a handheld radiofrequency spectroscopy results in lower re-excision rates, but local cancer recurrence rates are higher, the adequacy of the initial treatment must be questioned.

Handheld radiofrequency spectroscopy is used during breast cancer surgery, with outcomes of interest including immediate re-excision rate and long-term recurrence and survival rates after cancer detection.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- Comparative controlled prospective trials were sought, with preference for randomized controlled trials (RCTs).
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Pivotal Trial

The evidence evaluating the efficacy of MarginProbe comes from the pivotal trial by Allweis et al. (2008) that led to device approval by the U.S. Food and Drug Administration (FDA). (3-6) The reviewed trial reported the most relevant patient outcomes available for evaluating MarginProbe with the largest number of patients, including a large proportion of U.S. patients. In addition to clinical outcomes, the trial permitted assessments of diagnostic test performance of MarginProbe, which will inform judgments of its utility.

The pivotal trial, MarginProbe, a Device for Intraoperative Assessment of Margin Status in Breast Conservation Surgery (NCT00749931) compared surgical processes and short-term outcomes in patients undergoing lumpectomies for nonpalpable breast malignancies whose excised tissue was and was not assessed using MarginProbe. In both arms, surgeons could use standard of care intraoperative methods such as palpation, specimen imaging, and gross and/or microscopic pathology assessments. The pivotal trial was a multicenter (21 sites) randomized study of 596 patients assigned equally to both treatment arms. Enrolled patients met criteria described in the FDA labeling, but all also had non-palpable lesions that required image-guided localization. Trial design was complex and included several steps in sequence in which additional shavings of breast tissue could be taken during the operation. The principal outcome of the trial was complete surgical resection, in which positive margins were either re-excised or specifically noted if not re-excised. It was not necessary for the re-excision to result in a clear margin. This outcome is not fully clinically relevant.

For the principal outcome, surgeries using MarginProbe had a rate of successful surgical excision of 71.8% versus 22.4% for controls, with positive margin subjects as the denominator. The large magnitude of difference was statistically significant. However, this outcome was biased against the control group and included non-clinically relevant events as outcomes, such as positive margins not resected. The volume of tissue resected, on both a relative and an absolute scale, was greater in the MarginProbe group, but the trial only presents conclusions of a non-inferiority analysis without specifying the non-inferiority margin.

More clinically relevant outcomes included the proportion of patients with positive margins on final pathology after surgery, which was 31% for the MarginProbe group and 42% for the

control group (p=0.008). Some patients with positive margins in the MarginProbe group did not have positive margins in their main specimen on final pathology. However, due to false-positive MarginProbe readings, additional shavings were taken, and cancer tissue was found at the margin. Without these additional shavings in response to MarginProbe assessment, these patients would have been considered to have clear margins.

This occurrence reflects the uncertainty of final pathology in ascertaining whether all cancer tissue had been removed. The uncertainty complicated the comparison of outcomes between groups because a measure usually considered a poor outcome (e.g., positive margin), in this case, was not due to inadequate surgery but to inadvertent discovery of residual cancer due to false-positive MarginProbe readings.

Re-excision rates using all patients enrolled in the trial as the denominator showed about a 5% absolute reduction in the MarginProbe group (28.5% vs 23.8%), which was not statistically significant. The decision to reoperate was based on surgeon judgment of patient and tumor characteristics and the totality of pathologic findings. The trial did not assess outcomes beyond the short-term re-excision rate; thus, it is unknown whether the lower re-excision rates resulted in at least equivalent local recurrence rates. Without knowing whether recurrence rate is at least equivalent, a lower re-excision rate could reflect inadequate initial surgery.

The trial also reported the diagnostic characteristics of MarginProbe. Of 1788 margins with final histopathology, MarginProbe readings were valid or not missing in 1750 samples. Three hundred twenty-seven margins were positive, and MarginProbe was positive in 246, for a sensitivity of 75%. Of 1423 negative margins on final pathology, MarginProbe was negative in 660, for a specificity of 46%. These performance characteristics showing moderate sensitivity and poor specificity are consistent with better-than-random capability of the device in detecting positive margins. Given the 19% (327/1750) prevalence of positive margins, the positive predictive value of a positive MarginProbe test for a margin is 24%. In another analysis (performed or requested by the FDA) in which the location of the positive margin was ignored, and the test was considered positive if any margin tested positive, MarginProbe was 96% sensitive but only 9% specific. Although this test performance characteristic is less clinically relevant, the low specificity in this trial indicates that MarginProbe was positive for at least 1 margin in almost every patient in the trial, even though the prevalence of at least 1 positive margin was 52%.

Geha et al. (2020) reported single-center results for the Columbia cohort (n=46). (7) Following conventional lumpectomy and intraoperative assessment, margins in 23 patients were additionally evaluated with MarginProbe. Data were collected until the earliest of the following events: 2 months after last surgery, conversion to mastectomy, or initiation of chemotherapy. The re-excision rate in the device group was significantly lower compared to control (4.3% vs 34.8%; *P* = 0.022). The authors hypothesize that the device re-excision rate at their study site was lower than previously reported for the multicenter trial due to a higher number of patients with DCIS in the device group (30%) compared to control (8%) who were surgically-managed

with thicker tissue shavings in the case of device-reported margin involvement. Long-term excision and local recurrence rates were not reported for this cohort.

Systematic Reviews

A systematic review by Butler-Henderson et al. (2014) of techniques used for intraoperative assessment of margins in breast-conserving therapy for DCIS concluded that larger studies are needed to determine whether MarginProbe has a role to play in breast-conserving surgery. (8) This conclusion was based on the pivotal trial previously reviewed and earlier studies.

A systematic review by St John et al. (2017) of intraoperative techniques to assess margins following breast conservation surgery identified 55 studies, 35 of which were included in a meta-analysis. (9) The primary end point was diagnostic accuracy of the various techniques, which was based on pooled sensitivity, specificity, and area under the receiver operating characteristic curve. Reviewers found only one prospective study on MarginProbe, which was found to have a diagnostic accuracy of 68.2%, based in part on sensitivity (71.4%) and specificity (67.7%). Re-excision rates were a secondary outcome: of 57 patients in the MarginProbe study, 15.8% required re-excision during the initial surgery. The MarginProbe study was not included in the meta-analysis. Other intraoperative techniques included in the meta-analysis had pooled specificity ranging from 81% to 96%, depending on the modality, and pooled sensitivity ranging from 53% to 91%. The meta-analysis was limited by heterogeneity between studies in methodology and varying criteria for diagnosis and assessment of margins. A number of studies identified for the review could not be included in the meta-analysis because of missing raw data.

A systematic review by Gray et al. (2018) on intraoperative margin management in breast-conserving surgery identified 5 articles involving radiofrequency spectroscopy in a literature search conducted in July 2016. (10) The evidence for MarginProbe showed a 70% specificity. Higher false-positive rates result in higher volumes of tissue removal. When the authors considered the improved positive margin detection balanced with the limited specificity, they concluded that the routine use of MarginProbe was not recommended (grade 2B recommendation).

A systematic review with meta-analysis by Rossou et al. (2023) evaluated re-excision rates in studies of patients undergoing breast-conserving surgery for non-palpable DCIS or invasive breast cancer with intraoperative use of MarginProbe. (11) The authors included data from 4 RCTs and 8 nonrandomized studies comprising 2680 patients. Re-excision was reported in a mean of 10.93% (±5.49%) of patients whose evaluation included MarginProbe compared with 25.8% (±10.12%) of patients whose evaluation did not include use of MarginProbe (p=.001). Calculated mean specificity and sensitivity were 63.47% and 69.07%, respectively. Other clinical outcomes were not analyzed.

Nonrandomized Studies

Thill et al. (2014) reported on final results of a 2011 cohort study of MarginProbe in DCIS. (12, 13) Forty-two (76%) of 55 patients enrolled from the general screening population at 3 centers

in Germany were eligible for analysis. Patients underwent preoperative wire localization followed by breast-conserving surgery, with intraoperative assessment of the excised specimen by MarginProbe, radiograph, and paraffin-embedded pathologic review. MarginProbe was also used on additional shavings. Outcome measures were re-excision rate compared with a historical control rate of 39% and "procedure success," defined as 1) negative margins after breast-conserving surgery, and 2) early identification of an extended lesion, with conversion to mastectomy rather than re-excision. Criteria for re-excision defined a negative margin of 5 mm. The historical cohort comprised 67 patients with DCIS who underwent breast-conserving surgery by the same surgeons involved in the study during the year before enrollment began. Because information about patient selection and baseline data were not provided for either cohort, it is unknown how comparable the 2 cohorts were. Re-excision rate was 17%, a statistically significant difference from the historical control rate (p=0.018) with MarginProbe, and "procedure success" occurred in 24 (57%) of 42 patients. Sensitivity was 57% (95% confidence interval [CI], 48% to 66%) and specificity was 50% (95% CI, 42% to 58%). It is possible that the observed reduction in the re-excision rate was due to an increased incidence of mastectomies.

A retrospective, multicenter, before-after study by Sebastian et al. (2015) found a reduction in re-excision procedures from 26% to 10% after introduction of MarginProbe. (14) Investigators reviewed case records of 4 surgeons in 3 centers who used individual (non-standardized), routine lumpectomy methods including criteria for re-excision (186 cases before MarginProbe; 165 cases with MarginProbe). For each surgeon, re-excision rates using MarginProbe were compared to those from a historical set, comprising a consecutive series of cases shortly before each surgeon started using MarginProbe. With the device, there were 28 cases in which the margin on the main specimen was clear, but the corresponding shaving contained cancer. Three (1.8%) of 165 patients in the "after" group underwent mastectomy; the mastectomy rate in the "before" group was not reported. Performance characteristics (e.g., sensitivity, specificity) of MarginProbe cannot be calculated from these data. Other study limitations included lack of baseline description of the control ("before") group, potential confounding by secular trends over time, and lack of recurrence outcomes.

A retrospective single-center study by Blohmer et al. (2016) compared the use of MarginProbe in 150 patients to a historical control group of 172 patients. (15) The 2 groups had approximately similar proportions of patients with invasive breast cancer and DCIS. The historical control group underwent gross pathology examination and radiogram of the specimen as standard intraoperative procedures. The principal outcome of the study was re-excision rate. In patients for whom MarginProbe was used, the re-excision rate was 14.6%. In the historical control group, it was 29.7%. The study did not describe the criteria for re-excision, or include long-term patient outcomes. The difference in the amount of breast tissue removed between strategies was also not reported.

A retrospective single-center study by Coble et al. (2017) compared the use of MarginProbe in 137 patients to a historical control group of 199 patients. (16) The 2 groups had approximately similar demographic characteristics and proportions with invasive breast cancer and DCIS. The

historical control group underwent standard lumpectomy followed by additional shavings taken circumferentially from all aspects of the cavity. The principal outcome of the study was re-excision rate. For procedures using MarginProbe, the re-excision rate was 6.6%. In the historical control group, the rate was 15.1%. The total volume of tissue (main specimen plus additional shavings) removed was also less in the MarginProbe cases (78 cm^3 vs 116 cm^3; p=0.002).

Kupstas et al. (2017) retrospectively reviewed charts of patients from a single center who were treated with MarginProbe during lumpectomy for invasive carcinoma and DCIS; 120 patients were intraoperatively assessed using standard of care, and 120 patients were intraoperatively assessed using the MarginProbe device. (17) Reviewers found an improvement in the device group for the primary outcome, re-excision rate (9.2% of patients treated with MarginProbe required re-excision surgery vs 18.2% of those treated with standard of care; p=0.039). Included in this re-excision group were those who needed a second lumpectomy 5.8% (n=7) of the device group vs 15% (n=18) of the standard care group (p=0.020). The study population differed in initial specimen volume; the device group was with significantly smaller breast volume on average (p=0.032). It also differed in the number of shavings required, as those in the device group tended to receive 1.5 more shavings than their counterparts. The final mean volume of removed tissue was comparable between the device group (53.6 mL) and the standard of care group (53.5 mL; p=0.974). A study limitation included the absence of long-term outcomes.

Gooch et al. (2019) retrospectively reviewed charts of patients (n=341) from a single center who underwent breast-conserving surgery with the aid of the MarginProbe device during lumpectomy from 2013 to 2017 to elucidate the relationship between mammographic breast density and positive lumpectomy margins. (18) A main lumpectomy specimen served as the index lesion assessed via the device. The final margin status was defined as the conclusion of the surgery, taking into account any additional margins excised after removal of the main specimen with the aid of the MarginProbe device. Mammographic breast density was not correlated with the likelihood of a final positive margin (p=0.4564). Higher mammographic breast density was associated with younger age (p<0.0001) and lower body mass index (p<0.0001). The MarginProbe device identified 135 margin-positive main specimens. Final margins were positive in 34 (25.2%) patients and negative in 101 (74.8%) patients. The MarginProbe device identified 206 margin-negative main specimens. Final margins were positive in 17 (8.3%) and negative in 189 (91.7%) patients. These findings correspond to a sensitivity of 66.7% and a specificity of 65.2%. Positive margins on the main lumpectomy specimen were correlated with larger tumor size (p<0.001), more advanced disease stage at diagnosis (p=0.0247), the presence of a palpable mass (p=0.0010), and an increased likelihood of subsequent re-excision (p=0.0002). The overall re-excision rates were 11.3% and 8.0% for patients with BI-RADS category ratings of A-B or C-D, respectively.

A prospective single-center study by LeeVan et al. (2020) compared the use of MarginProbe for breast-conserving surgery in 60 patients with a historical control group. (19) Intraoperative margin assessment was performed with a surgical standard operating procedure consisting of specimen radiography and gross pathological examination. Re-excision surgery was defined as a return to the operating table for a subsequent procedure. However, criteria for re-excision

surgery were not provided. While 8 patients (13.3%) had a final close or positive margin on pathology following use of MarginProbe, only 4 patients consented to re-excision surgery, yielding a re-excision rate of 6.6%. Four patients declined re-excision in favor of whole breast irradiation. Although this result was statistically lower compared to the historical re-excision rate of 8.6% ($p<0.01$), the authors conclude that this difference is not clinically meaningful. The sensitivity, specificity, negative predictive value, and positive predictive value for the use of MarginProbe was 67%, 60%, 16%, and 94%, respectively, which was similar to standard protocol alone. Long-term outcomes and complete demographic characteristics for each group were not reported.

Cen et al. (2021) published a retrospective review of patients in a single center's institutional breast cancer database who received both neoadjuvant chemotherapy and breast-conserving surgery (N=61) between 2010 and 2018. (20) Median patient age was 51.8 years and the study population had diverse representation (White 43%, Black or African American 17%, Hispanic 24%, and Asian 17%). A complete response was achieved for 19 (31.1%) patients. Of the remaining 42 patients, 9 (21%) had margins that required re-excision. While the use of MarginProbe was associated with a lower re-excision rate (6% vs. 31%, respectively), this difference was not statistically significant. Long-term outcomes were not reported.

Hoffman et al. (2022) conducted a prospective cohort study of patients undergoing breast-conserving surgery with the use of MarginProbe (N=48) in a single-center general surgery department between 2018 and 2019. (21) Of the 48 patients included in the study, there were 51 total tumors analyzed. Out of 306 margins (in 51 tumors), 4 were not assessed by MarginProbe. MarginProbe correctly identified 3 of 13 positive margins; it also read 97 false positive readings of 289 true negative margins. These findings correspond to a sensitivity of 23.1% (95% CI, 5.0% to 53.8%), specificity of 66.4% (95% CI, 60.7% to 71.9%), positive predictive value of 3.0% (95% CI, 0.6% to 8.5%), and negative predictive value of 95.1% (95% CI, 91.1% to 97.6%).

Haney et al. (2024) conducted a single-center prospective cohort study of patients undergoing partial mastectomies with the MarginProbe (n=153) compared to patients who received standard care partial mastectomies (n=300). (22) The study assessed the effectiveness of the MarginProbe in reducing re-excisions compared to standard care. The study reported that MarginProbe reduced the likelihood of re-excision by 58% ($p<0.001$). However, its use resulted in a greater shave volume, with an average of 9.8 cc more tissue removed compared to the standard care ($p<0.001$). MarginProbe showed a sensitivity of 70.1% and a specificity of 47.5%.

Key limitations in relevance, design, and conduct of the identified studies are summarized in Tables 1 and 2.

Table 1. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Compartor[c]	Outcomes[d]	Duration of Follow-Up[e]

Thill et al. (2014) (12)				1. Re-excision rate is an intermediate outcome 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Sebastian et al. (2015) (14)				1. Re-excision rate is an intermediate outcome 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Blohmer et al. (2016) (15)				1. Re-excision rate is an intermediate outcome 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Coble et al. (2017) (16)				1. Re-excision rate is an intermediate outcome 3. Key clinical validity outcomes not	1. Long-term outcomes not reported

				reported (sensitivity, specificity and predictive values)	
Kupstas et al. (2017) (17)				1. Re-excision rate is an intermediate outcome 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Gooch et al. (2019) (18)				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported
LeeVan et al. (2020) (19)				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported
Cen et al. (2021) (20)				1. Re-excision rate is an intermediate outcome 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values)	1. Long-term outcomes not reported
Hoffman et al. (2022) (21)					1. Long-term outcomes not reported
Haney et al. (2024) (22)				1. Re-excision rate is an intermediate outcome	1. Long-term outcomes not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 2. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Thill et al. (2014) (12)	1. Information about patient selection and baseline data were not provided for either cohort					
Sebastian et al. (2015) (14)	1. There is a lack of baseline selection and description of the control group					
Blohmer et al. (2016) (15)			3. Did not describe the criteria for re-excision			
Coble et al. (2017) (16)						
Kupstas et al. (2017) (17)						

Gooch et al. (2019) (18)						
LeeVan et al. (2020) (19)	1. Complete demographic characteristic information and selection criteria for each group were not reported		3. Did not describe the criteria for re-excision			
Cen et al. (2021) (20)			3. Did not describe the criteria for re-excision			
Hoffman et al. (2022) (21)	1. Complete demographic characteristic information and selection criteria for each group were not reported					
Haney et al. (2024) (22)	2. Retrospective nature of the standard of care data collection and prospective nature of the MarginProbe cohort					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High

number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No evidence was identified supporting the long-term utility of MarginProbe when used to assess surgical margins during lumpectomy for localized breast cancer or DCIS.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Current evidence does not support the clinical validity of MarginProbe; hence a chain of evidence cannot be constructed.

Section Summary: Handheld Radiofrequency for Breast Cancer Margin Detection

Although these nonrandomized studies showed a reduction in re-excision rate when using MarginProbe compared to historical controls, they were not rigorously controlled. Moreover, re-excision rate is an intermediate outcome that is only valid if long-term patient outcomes (e.g., recurrence rate) are equivalent between MarginProbe and the alternative strategy. The single RCT comparing short-term outcomes for patients undergoing breast surgery for non-palpable breast malignancies managed with and without MarginProbe reported no significant difference in re-excision rates between the 2 trial arms. In addition, both the sensitivity and specificity rates for the MarginProbe were lower than those for the current standard best practices.

Summary of Evidence

For individuals who have localized breast cancer or ductal carcinoma in situ undergoing breast-conserving surgery (lumpectomy) who are evaluated with handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins (e.g., MarginProbe), the evidence includes a randomized trial, several historical control studies, and systematic reviews. Relevant outcomes are change in disease status and morbid events. In the randomized trial, histologic examination of surgical margins was not used in the control arm. The outcome measure (complete surgical resection) was not directly clinically relevant and was biased against the control arm, and patient follow-up was insufficient to assess local recurrence rates.

The difference in re-excision rates between the 2 trial arms was not statistically significant. Diagnostic characteristics of the device showed only moderate sensitivity and poor specificity; thus, the device will miss some cancers and provide frequent false-positive results. Although several historical control studies have shown lower re-excision rates among patients in whom MarginProbe was used, the studies lacked adequate rigor to demonstrate whether the outcomes are attributable to MarginProbe. The studies did not report recurrence outcomes, which is important for assessing adequacy of resection. A randomized trial that assesses recurrence rates is required to evaluate whether the net health outcome improves with handheld radiofrequency spectroscopy compared with standard intraoperative surgical margin evaluation, including histologic techniques. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Society of Breast Surgeons

In 2015, the most current version of the American Society of Breast Surgeons performance and practice guidelines for breast-conserving surgery mention that specimens should be submitted for margin assessment either intraoperatively or post-surgically, depending on each institution's protocol. A recommendation for a specific margin assessment method over another was not made. (23)

In 2024, the American Society of Breast Surgeons issued a resource guideline for breast cancer surgery margins for re-excision surgery after lumpectomy or breast conservation for invasive or in-situ breast cancer. (24) The guideline does not include recommendations for the intraoperative assessment of surgical margins via radiofrequency spectroscopy.

National Comprehensive Cancer Network (NCCN)

Current (v.3.2025) NCCN guidelines for breast cancer do not include recommendations for intraoperative assessment of surgical margins using radiofrequency spectroscopy for ductal carcinoma in situ or invasive breast cancer. (25)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might impact this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT02774785	Reducing Re-excisions After Breast Conserving Surgery: A Randomized Controlled Trial Comparing the MarginProbe Device in Addition to Standard Operating Procedure Versus Standard Operating Procedure Alone in Preventing Re-excision	127	Feb 2021 (completed)

NCT02406599[a]	MarginProbe® System U.S. Post-Approval Study Protocol CP-07-001	440	Nov 2021
NCT00625417	Optical Spectroscopy in Evaluating Tumor Margins in Patients Who Have Undergone Surgery for Breast Tumors	180	Dec 2021

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	19499, 0546T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Schnitt SJ, Moran MS, Giuliano AE. Lumpectomy Margins for Invasive Breast Cancer and Ductal Carcinoma in Situ: Current Guideline Recommendations, Their Implications, and Impact. J Clin Oncol. Jul 10 2020; 38(20):2240-2245. PMID 32442067
2. Maloney BW, McClatchy DM, Pogue BW, et al. Review of methods for intraoperative margin detection for breast conserving surgery. J Biomed Opt. Oct 2018; 23(10):1-19. PMID 30369108
3. Schnabel F, Boolbol SK, Gittleman M, et al. A randomized prospective study of lumpectomy margin assessment with use of MarginProbe in patients with nonpalpable breast malignancies. Ann Surg Oncol. May 2014; 21(5):1589-1595. PMID 24595800
4. Rivera RJ, Holmes DR, Tafra L. Analysis of the Impact of Intraoperative Margin Assessment with Adjunctive Use of Marginprobe versus Standard of Care on Tissue Volume Removed. Int J Surg Oncol. 2012; 2012:868623. PMID 23326653
5. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): MarginProbe System (2012). Available at <https://www.accessdata.fda.gov> (accessed January 1, 2025).
6. Allweis TM, Kaufman Z, Lelcuk S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. Am J Surg. Oct 2008; 196(4):483-489. PMID 18809049

7. Geha RC, Taback B, Cadena L, et al. A Single institution's randomized double-armed prospective study of lumpectomy margins with adjunctive use of the MarginProbe in nonpalpable breast cancers. Breast J. Nov 2020; 26(11):2157-2162. PMID 32772474
8. Butler-Henderson K, Lee AH, Price RI, et al. Intraoperative assessment of margins in breast conserving therapy: a systematic review. Breast. Apr 2014; 23(2):112-119. PMID 24468464
9. 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. Feb 2017; 265(2):300-310. PMID 27429028
10. Gray RJ, Pockaj BA, Garvey E, et al. Intraoperative Margin Management in Breast-Conserving Surgery: A Systematic Review of the Literature. Ann Surg Oncol. Jan 2018; 25(1):18-27. PMID 28058560
11. Rossou C, Alampritis G, Patel B. Reducing re-excision rates in breast conserving surgery with Margin Probe: systematic review. Br J Surg. Jan 03 2024; 111(1):znad335. PMID 37991190
12. Thill M, Dittmer C, Baumann K, et al. MarginProbe®--final results of the German post-market study in breast conserving surgery of ductal carcinoma in situ. Breast. Feb 2014; 23(1):94-96. PMID 24291375
13. Thill M, Röder K, Diedrich K, et al. Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy. Breast. Dec 2011; 20(6):579-580. PMID 21885281
14. Sebastian M, Akbari S, Anglin B, et al. The impact of use of an intraoperative margin assessment device on re- excision rates. Springerplus. 2015; 4:198. PMID 26020017
15. Blohmer JU, Tanko J, Kueper J, et al. MarginProbe© reduces the rate of re-excision following breast conserving surgery for breast cancer. Arch Gynecol Obstet. Aug 2016; 294(2):361-367. PMID 26796680
16. Coble J, Reid V. Achieving clear margins. Directed shaving using MarginProbe, as compared to a full cavity shave approach. Am J Surg. Apr 2017; 213(4):627-630. PMID 28049561
17. Kupstas A, Ibrar W, Hayward RD, et al. A novel modality for intraoperative margin assessment and its impact on re-excision rates in breast conserving surgery. Am J Surg. Mar 2018; 215(3):400-403. PMID 29191356
18. Gooch JC, Yoon E, Chun J, et al. The Relationship of Breast Density and Positive Lumpectomy Margins. Ann Surg Oncol. Jun 2019; 26(6):1729-1736. PMID 30888516
19. LeeVan E, Ho BT, Seto S, et al. Use of MarginProbe as an adjunct to standard operating procedure does not significantly reduce re-excision rates in breast conserving surgery. Breast Cancer Res Treat. Aug 2020; 183(1):145-151. PMID 32607640
20. Cen C, Chun J, Kaplowitz E, et al. Margin Assessment and Re-excision Rates for Patients Who Have Neoadjuvant Chemotherapy and Breast-Conserving Surgery. Ann Surg Oncol. Sep 2021; 28(9):5142-5148. PMID 33635409
21. Hoffman A, Ashkenzai I. The efficiency of MarginProbe in detecting positive resection margins in epithelial breast cancer following breast conserving surgery. Eur J Surg Oncol. Jul 2022; 48(7):1498-1502. PMID 35219544
22. Haney V, Lee SM, Goldman J, et al. Evaluating the Effect of MarginProbe® Use on Re-excisions After Partial Mastectomy: A Single-Institution Analysis. Ann Surg Oncol. Nov 2024; 31(12):8068-8075. PMID 39090489

23. American Society of Breast Surgeons. Performance and Practice Guidelines for Breast-Conserving Surgery/Partial Mastectomy (2015). Available at <https://www.breastsurgeons.org> (accessed January 2, 2025).
24. American Society of Breast Surgeons. Resource Guide: Breast Cancer Breast Conservation Surgery Margins (2024). Available at <https://www.breastsurgeons.org> (accessed April 3, 2025).
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2025. Available at <https://www.nccn.org> (accessed April 3, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
06/15/2025	Document updated with literature review. Coverage unchanged. Added/updated the following references: 22, 24, and 25.
09/15/2024	Document updated with literature review. Coverage unchanged. Added/updated the following references: 1, 11, and 24.
01/01/2024	Document updated with literature review. Coverage unchanged. Added/updated the following references: 18, 19, and 22.
05/15/2022	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. Added/updated the following references: 7, 17, 18 and 21.
09/15/2020	Reviewed. No changes.
09/15/2019	Document updated with literature review. Coverage unchanged. References 1, 8, 9, and 15-17 added/updated.
06/15/2018	Reviewed. No changes.
01/01/2018	New medical document. Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered experimental, investigational and/or unproven.