Description

Breast-conserving surgery as part of the treatment of localized breast cancer is optimally achieved by attaining margins around the surgical resection that are free of tumor cells. Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins (i.e., MarginProbe®) is intended to increase the probability that the surgeon will achieve clear margins in the initial operation, thus avoiding the need for a second surgery to excise more breast tissue.

Related Policies

- N/A

Policy

Handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast-conserving surgery is considered investigational.

Policy Guidelines

There is no specific CPT code for this spectroscopic assessment.

The following unlisted CPT code may be used:

- 19499: Unlisted procedure breast

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent that there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Rationale

Background

Breast-conserving surgery as part of the treatment of localized breast cancer is optimally achieved by attaining margins around the surgical resection that are free from tumor cells. Failure to achieve clear margins will often require additional surgery to re-excite breast tissue. Currently, histologic examination of excised tissues after completion of surgery is the only method of definitively determining 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.

MarginProbe® is a device based on the principles of radiofrequency spectroscopy that measures 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 resected surgical specimen and analyzes the tissue as to whether it is likely malignant or benign. During the operation, the surgeon touches the MarginProbe® device to each surface of the biopsy specimen. The device gives a reading of positive or negative for each touch. If any one of the touches on a particular margin gives a positive reading, the margin is considered to be positive and should be re-excised if possible. The device can only be used on the main lumpectomy specimen, and cannot be used on shavings or in the lumpectomy cavity in the patient's breast. Use of the MarginProbe® device is intended to increase the probability that the surgeon will achieve clear margins in the initial operation, thus avoiding the need for a second surgery to excise more breast tissue.

Regulatory Status

In January 2013, MarginProbe® received premarket approval (PMA) approval from the Food and Drug Administration (FDA). The Dune MarginProbe®™ System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1 mm) of the main ex-vivo lumpectomy specimen after primary excision and 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. PMA product code: OEE.

Rationale

Evidence evaluating the efficacy of MarginProbe® comes from the pivotal trial that led to Food and Drug Administration (FDA) approval.2-4 An earlier study evaluating its use did not use the same classification algorithm and may not represent the current performance of the device.5 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 allows assessments of diagnostic test performance of MarginProbe®, which will help inform judgments of its utility.

The pivotal trial (NCT00749931) compared surgical processes and short-term outcomes in patients in whom MarginProbe® was used versus patients in whom margin probe was not used. The control strategy did not include intraoperative histologic techniques but did include radiographic imaging of the main resection specimen in addition to inspection and palpation of the resection specimen. The pivotal trial was a multicenter (21 sites) randomized trial of 596 patients assigned equally to the 2 treatment arms. Enrolled patients met criteria described in FDA labeling, but also all had nonpalpable 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 declared principal outcome of the trial was called complete surgical resection, in which positive margins were either re-excised or noted if not re-excised. It was not necessary for the re-excision to result in a clear margin. Thus, this outcome is not fully clinically relevant and appears to be biased against the control arm of the trial.

For the principal outcome of complete surgical resection, MarginProbe® showed a rate of 71.8% versus 22.4% for controls, with positive margin subjects as the denominator, which is a large magnitude of difference and statistically significant. However, this outcome is biased against the control group and includes nonclinically relevant events as outcomes, such as positive margins that were not resected. Volume of tissue resected on both a relative and absolute scale were greater in the MarginProbe® group, but data analysis only presents conclusions of a noninferiority analysis. The noninferiority margin for the normalized total tissue volume was not specified.

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% in the control group (p=0.008). Some patients with positive margins in the MarginProbe® group did not have positive margins in their main specimen. 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 a clear margin. This occurrence reflects the uncertainty of final pathology in trying to ascertain whether all cancer tissue has been removed. It complicates the comparison of outcomes between the 2 groups because a measure usually considered a poor outcome such as a positive margin, in this case, is not due to inadequate surgery but 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 outcome of re-excision rate; thus, it is unknown whether the lower re-excision rate 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. Three hundred twenty-seven margins were positive, and MarginProbe® was positive in 246, for a sensitivity of 75.2%. Of 1423 negative margins, MarginProbe® was negative in 660, for a specificity of 46.4%. 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 (apparently performed or requested by FDA) in which the location of the positive margin was ignored, and the test was considered positive if any margin tested positive, MarginProbe® was 96.3% sensitive but only 8.9% 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%.

A 2014 systematic review of techniques used for intraoperative assessment of margins in breast conserving therapy for ductal carcinoma in situ (DCIS) concluded that larger studies are needed to determine whether MarginProbe® has a role to play in breast-
conserving surgery. This conclusion was based on the pivotal trial reviewed above and earlier studies.

In 2014, Thill et al reported final results of a cohort study of MarginProbe® in DCIS. 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® also was 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 (Fisher exact test, p=0.018), and “procedure success” occurred in 24 (57%) of 42 patients. Sensitivity was 57% (95% CI: 48 to 66), and specificity was 50% (95% CI: 42 to 58). It is possible that the observed reduction in the reduced re-excision rate was due to an increased incidence of mastectomies. A randomized trial that assesses recurrence is required to demonstrate improvement in net health outcome with MarginProbe®.

Section Summary

The pivotal trial showed a nonstatistically significant difference in re-excision rate in the 2 trial arms. The declared principal outcome of the trial, complete surgical resection, is not directly clinically relevant and is biased against the control arm of the trial. The trial did not follow patients long enough to assess the local recurrence rate, which would be important for evaluating the adequacy of initial excision. Diagnostic characteristics of the device showed only moderate sensitivity and poor specificity; thus, the device will miss some cancers and have frequent false-positive results. A subsequent study in women with DCIS showed poor sensitivity and specificity and suggested that more mastectomies may be performed with MarginProbe®. A randomized trial that assesses recurrence is required to demonstrate whether net health outcome is improved.

Ongoing and Unpublished Clinical Trials

No ongoing studies of MarginProbe® for assessment of surgical margins during breast conservation surgery are currently listed online at ClinicalTrials.gov.

Summary

Two clinical studies of MarginProbe® provide insufficient evidence that the device improves initial surgical treatment of localized breast cancer or ductal carcinoma in situ (DCIS). The device has not been assessed in comparison with other techniques of intraoperative margin assessment. Lacking evidence for improved net health outcomes, use of handheld radiofrequency spectroscopy for intraoperative assessment of surgical margins during breast conservation surgery is considered investigational.
Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network


U.S. Preventive Services Task Force Recommendations

Use of handheld radiofrequency spectroscopy is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

Documentation Required for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services are considered investigational and therefore not covered for any indication.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT®</td>
<td>See Policy Guidelines</td>
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<tr>
<td></td>
<td>19499</td>
<td>Unlisted procedure, breast</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>11/26/2014</td>
<td>BCBSA medical policy adoption</td>
<td>Medical Policy Committee</td>
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</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.
**Medical Policy**

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements**

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.