

Submitted by:

Dennis Holmes, MD  
Medical Advisor  
Dune Medical, Inc.  
6120 Windward Parkway  
Suite 160  
Alpharetta, GA 30005  
Phone: 855-597-3863  
Email: [drholmesmd@me.com](mailto:drholmesmd@me.com)

Date of Request: July 05, 2018

**NCCN Guidelines Panel: Breast Cancer**

On behalf of Dune Medical, I respectfully request the NCCN Breast Cancer Panel to review the enclosed data for inclusion of radiofrequency spectroscopy (MarginProbe) in the 'Margin Status Recommendation for DCIS and Invasive Breast Cancer'.

**Specific Changes:** Request to recommend intraoperative margin assessment using radiofrequency spectroscopy to breast cancer guidelines.

BINV-F: Margin Status Recommendations for DCIS and Invasive Breast Cancer

*Add: Margins should be evaluated intraoperatively on all surgical specimens from breast conserving surgery (BCS). Recommendations for optimal intraoperative specimen evaluation include intraoperative imaging, radiofrequency spectroscopy or full cavity shave.*

DCIS-1 and BINV-2: Include in footnote references to lumpectomy (both DCIS & invasive)

*Among patients undergoing lumpectomy, there is a ~ 25% rate of re-excision due to positive margins. This rate can be improved by use of intraoperative imaging, radiofrequency spectroscopy or full cavity shave.*

**FDA Status:** The MarginProbe Radiofrequency Spectroscopy System was FDA PMA Approved in Dec. 2012. This technology is an adjunctive diagnostic tool for identification of cancerous tissue at the margins of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use in conjunction with standard methods (such as intraoperative imaging and palpation) in patients undergoing breast lumpectomy surgery for previously diagnosed breast cancer.

**Rationale:**

Over 300,000 women are diagnosed with invasive or in-situ cancer each year in the US. A majority of newly diagnosed patients are appropriate candidates for breast conserving surgery, with approximately 200,000 undergoing the procedure each year. Unfortunately, 40,000-50,000 women undergoing breast conserving surgery must undergo a reoperation largely due to positive margins which are not detected until histopathology performed after surgery.

While the 2014 SSO/ASTRO Margin Guideline for Invasive Breast Cancer and the 2016 SSO/ASTRO/ASCO Guideline for DCIS, which are recommended within the NCCN Breast Cancer Guidelines, have had an impact on reducing re-excision rates (8%-26% reduction), the rate of re-excision continues to vary widely, with invasive cancer remaining close to 20%<sup>1</sup>, and re-excision rates in DCIS often higher than 30%.

---

<sup>1</sup> Chavez-MacGregor M, et al. Impact of the SSO ASTRO consensus guidelines on invasive margins on the re-excision rate among patients undergoing breast conserving surgery (BCS). *Cancer Research*. 2018; 78(4): P2-12-03

Re-excision carries physical, emotional and financial burden for the patient and the healthcare system. Such negative consequences of additional surgery include increased anxiety, increased volumes of tissue excised leading to compromised cosmetic outcome, delay in treatment pathway and onset of adjuvant treatments, increased surgery related complications, and increased need for oncoplastic surgeries. Women who undergo a re-excision face a 38% increase in complications associated with the additional surgery<sup>2</sup>. In addition, data reports that ~10% of women who are faced with a re-excision will convert to mastectomy<sup>3</sup>, bringing further cost, complications and extension in treatment timeline. Recently published cost and complication data on repeat breast-conserving surgeries using commercial claims data reports that the mean added health care cost due to a repeat surgery is \$16,072 per patient<sup>4</sup>.

While current 2018 NCCN Breast Cancer Guidelines acknowledge the importance of achieving pathologically negative margins after breast conserving surgery resection, there are no recommendations on methods for achieving pathologically negative margins during the time of lumpectomy.

*Per MS-19: After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN Panel notes that the benefit of lumpectomy is predicated on achieving pathologically negative margins after resection.*

Additionally, the 'Margin Status Recommendation for DCIS and Invasive Breast Cancer' is focused on histopathologic margin evaluation, and does not provide guidance on microscopic, intraoperative evaluation of margins. This fails to provide the opportunity to reduce positive margin rates at the time of surgery and thus defers margin evaluation to the post-operative period.

MarginProbe is a technology that uses radiofrequency spectroscopy to identify microscopic cancer at the surgical margin *during* breast conserving surgery, allowing the surgeon to take directed shaves, clear the margin, and improve oncologic outcome at the time of initial surgery. Used as an adjunct to standard intraoperative margin assessment methods (palpation, specimen radiography), MarginProbe has been shown to significantly reduce positive margin rates which has translated into a consistent reduction in re-excision rates of over 50%, regardless of the margin guideline being used. Use of radiofrequency spectroscopy intraoperatively does not obviate the need for histological assessment of the resection margin post-operatively.

**Precedent for this Request:**

The precedent for this request for technical guidance on achievement of clear margins is the inclusion of technical guidance for the optimal method of intraoperative node assessment of nodes positive women treated with neoadjuvant chemotherapy (BINV-11). In both cases, these measures are supported by prospective clinical trials (Margin Probe Radiofrequency Spectroscopy, Level Ib), ACOSOG Z1071 Trial, Level IIa).

Dennis Holmes, MD, FACS



Dennis R. Holmes (Jul 6, 2018)

Jul 6, 2018

---

<sup>2</sup> Metcalfe LN, et al. Looking beyond the margins: Economic costs and complications associated with repeated breast conserving surgeries. San Antonio Breast Cancer Symposium 2016.

<sup>3</sup> Morrow M, et al. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. *JAMA*. 2009 Oct 14;302(14):1551-6.

<sup>4</sup> Metcalfe LN, et al. Beyond the margins: Economic costs and complications associated with repeated breast conserving surgeries. *JAMA Surgery*: 2017; E1-E2

**The following Radiofrequency Spectroscopy peer reviewed publications are submitted in support of this proposed change:**

1. Pappo I, Spector R, Schindel A, et al. Diagnostic Performance of a Novel Device for Real-Time Margin Assessment of Lumpectomy Specimens. *Journal of Surgical Research*. 2010;160: 277-281
2. 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*. 2008; 196: 483-89
3. Thill M, et al. MarginProbe - Final results of the German post market study in breast conserving surgery of ductal carcinoma in situ. *The Breast*. 2014; 23: 94-6.
4. Schnabel F, et al. A Randomized Prospective Study of Lumpectomy Margin Assessment with Use of MarginProbe in Patients with Nonpalpable Breast Malignancies. *Ann Surg Oncol*. 2014; 21:1589-95
5. Sebastian M, Akbari S, Anglin B, et al. The impact of use of an intraoperative margin assessment device on re excision rates. *SpringPlus*. 2015; 4:198
6. Blohmer J, et al. MarginProbe reduces the rate of re excision following breast conserving surgery for breast cancer. *Arch Gynecol Obstet*. 2016;294(2):361-7
7. Coble J, Reid V. Achieving clear margins. Directed shaving using MarginProbe, as compared to a full cavity shave approach. *Am J Surg*. 2016
8. Kupstas A, et al. A novel modality for intraoperative margin assessment and its impact on re-excision rates in breast conserving surgery. *Am J Surg*. 2018; 215:400-403

**Additional documentation submitted in support of this proposed change:**

- Reduction in Re-excision: MarginProbe Radiofrequency Spectroscopy vs. SSO-ASTRO Guidelines
- Do All Positive Margins in Breast Cancer Patients Undergoing Partial Mastectomy Need to be Resected? *J. Am Coll Surg*. 2018; 227: 13-21.