Bioimpedance measurement as an assessment of margin positivity in Mohs surgical specimens of non-melanoma skin cancer: Management implications

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Non-melanoma skin cancer (NMSC) is responsible for significant morbidity, with squamous cell carcinoma also potentially causing mortality.[1] Mohs micrographic surgery (MMS) has become the standard of care for high-risk lesions, but the need for histopathologic margin assessment at each stage significantly adds to the procedural duration, particularly in multi-stage cases.

Bioimpedance spectroscopy is a novel *ex-vivo* technique that relies on differing flow of electric current through diverse tissue types (such as muscle and fat)—a property related to varying water and electrolyte compositions of cellular components.[2] It has been used to measure total body water, detect lymphedema, and differentiate benign from malignant lesions.[2] This technology has also been applied to intraoperative surgical margin assessment for urologic malignancies.[3] However, it has not yet been applied to margin evaluation in NMSC.

We assessed the sensitivity and specificity of bioimpedance (compared to frozen-section histology) for detecting the presence of malignant cells in the margins of MMS specimens of NMSC.

One-hundred fifty-one specimens from 55 primary malignancies in 50 consecutive patients undergoing MMS for NMSC were assessed comparing *ex-vivo* bioimpedance spectroscopy (MarginScan, NovaScan LLC., Milwaukee, WI) with traditional frozen-section histopathologic methods (Figure 1, Table 1). IRB approval was obtained. Bioimpedance measurements were performed and the results were fit to a Cole-Cole function curve to obtain Cole relaxation frequencies.[4] Based on the results, each specimen was labeled as “unlikely” or “likely” to contain malignant cells in the margins, according to previously-described parameters.[4] Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) for bioimpedance were calculated by comparing the results to histopathologic findings.

Forty-four out of 151 MMS specimens (29%) displayed positive margins by histopathologic analysis, while 45 (30%) were probable for margin positivity by bioimpedance. Overall, 148/151 (98%) specimens displayed concordant results between histopathology and bioimpedance. Three discordant specimens representing one false positive and two false negative bioimpedance measurements were noted (Figure 2). Sensitivity and specificity of bioimpedance were 95.6% and 99.1%, respectively. PPV and NPV were 97.7% and 98.1%.

The rate-limiting step of MMS is the preparation and assessment of frozen-sections at each procedural stage, which requires 20-45 minutes for an average procedure but can be much longer for complex cases.[5] In contrast, bioimpedance only requires seven seconds per measurement (with approximately 20.5 separate measurements required for complete margin assessment per Mohs stage, totaling 2 minutes, 23 seconds on average). Therefore, these findings suggest that bioimpedance may have the potential to reduce case time by eliminating the need to process negative specimens while maintaining high diagnostic accuracy.

Study limitations include small sample size, single surgeon, and that all lesions were already biopsy-proven NMSCs. However, since MMS is only typically performed on malignancy-confirmed lesions, this sample is representative of real-world practice. Additionally, SCCs and BCCs were analyzed together due to the small sample size. In the future, studies separately analyzing bioimpedance for detection of SCC and BCC in MMS specimens could be beneficial.

Larger multicenter studies are suggested to increase generalizability of these results. However, these preliminary data suggest that bioimpedance may provide an expedient, novel approach for evaluating the presence of malignant cells in MMS NMSC specimens, thereby making the process more efficient without loss of efficacy.

References

1. Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *European journal of cancer (Oxford, England : 1990).* 2015;51(14):1989-2007.
2. Braun RP, Mangana J, Goldinger S, French L, Dummer R, Marghoob AA. Electrical Impedance Spectroscopy in Skin Cancer Diagnosis. *Dermatologic clinics.* 2017;35(4):489-493.
3. Khan S, Mahara A, Hyams ES, Schned AR, Halter RJ. Prostate Cancer Detection Using Composite Impedance Metric. *IEEE transactions on medical imaging.* 2016;35(12):2513-2523.
4. Shell J, Gregory WD. A cancer detection device utilizing multi-tiered neural networks for improved classification. Paper presented at: Healthcare Innovation Point-Of-Care Technologies Conference (HI-POCT), 2016 IEEE2016.
5. Longo C, Gardini S, Piana S, et al. Ex Vivo Fluorescence Microscopy: Clinical Applications in Dermatology and Surgical Pathology. In: Hamblin MR, Avci P, Gupta GK, eds. *Imaging in Dermatology.* Academic Press; 2016:95-102.

Abbreviations

NSCM, non-melanoma skin cancer

IRB, institutional review board

MMS, Mohs micrographic surgery

PPV, Positive predictive value

NPV, Negative predictive value

US, United States

77 **Figure Legends**

78 Figure 1. Sample specimen cassette for impedance spectroscopy device

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80 Figure 2. Distribution of Cole Frequencies of 151 Mohs specimens of non-melanoma skin
81 cancer, stratified by histopathologic and bioimpedance results

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Tables

Table 1. Diagnosis and location of included lesions

Lesion Location	# Cases BCC 43 Total (78%)	# Cases SCC 12 Total (22%)	Total # Cases
Nose	15	1	16
Cheek	9	2	11
Ear	4	2	6
Scalp	3	2	5
Lip	5	0	5
Forehead/Temple	2	2	4
Chin	2	0	2
Finger	0	2	2
Neck	1	0	1
Back	0	1	1
Shin	1	0	1
Shoulder	1	0	1

SCC = Squamous cell carcinoma, BCC = Basal cell carcinoma, # = number, % = Percent