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Annals of Oncology Case Reports

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Use of Targeted Osmotic Lysis for the Treatment of Malignant Melanoma: Case Report

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Received: Feb 17, 2025

Accepted: Mar 07, 2025

Published Online: Mar 15, 2025

Journal: Annals of Oncology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Targeted osmotic lysis; Malignant melanoma; Sodium channels; Sodium pumps; Pulsed electric fields; Case report

Abstract

Malignant melanomas are often misdiagnosed or discounted when the disease is present in early, more treatable stages. When present during later stages of disease treatment options tend to be more limited, less effective, and prone to association with significant adverse effects. This report presents observations made when Targeted Osmotic Lysis (TOL), a novel method recently introduced as a method for treating late-stage carcinomas was used to treat a patient with malignant melanoma that was found to highly express Voltage-Gated Sodium Channels (VGSCs). The patient underwent 3 cycles of TOL therapy, i.e., digoxin loading to a therapeutic steady-state level, then exposure to pulsed electric field stimulation for 2 hours on 2 consecutive days. The patient experienced no adverse effects from the treatment and realized complete resolution of the primary lesion without residual scarring. Magnetic resonance imaging of the area that contained the primary lesion and areas that are frequently targets of melanotic metastasis arising from facial lesions revealed no evidence of residual tumor or metastatic development. The results in this report provide further evidence to justify consideration of TOL as an option for treating many forms of carcinoma that over-express VGSCs.

Introduction

Cancer is a group of diseases that is characterized by alterations in cell functions responsible for controlling cell growth and reproduction, the process of programmed cell death that is essential for maintaining normal cell function, turnover, and repair, and an enhanced ability to mutate in order to ensure cell survival [1,2]. Malignant melanomas are forms of skin cancer that are particularly problematic for diagnosis and management because, compared to other forms of skin cancer, they are rare, generally small, aggressive, frequently present in hard to visualize areas, vary significantly in their spatial, temporal, and morphological presentation, and are often similar in appearance to other benign, pigmented structures in the skin. Phenotypic heterogeneity and genetic heterogeneity of the various forms of cancer, are responsible for unique characteristics of each tumor that impose complications that limit the range of treatment effectiveness. This often dictates the need for personalized therapeutic management when attempting to identify and deliver treatment for the broad spectrum of neoplastic disease [3]. Despite the uniqueness of lesions that comprise individual neoplastic disease, recent reports detailing the use of Targeted Osmotic Lysis (TOL), a novel method for treating late stage carcinomas, have provided evidence that may make it possible to provide a safe and well-tolerated method for treating a wide range of cancers that over-express Voltage-Gated Sodium Channels (VGSCs) and sodium, potassium ATPase (Na^+, K^+-ATPase; sodium pumps) [4-7]. The over-expression of these proteins is an essential mechanism that imparts enhanced can-

Cite this article: Gould HJ, Dahiya RS, Sims A, Paul D. Use of Targeted Osmotic Lysis for the Treatment of Malignant Melanoma: Case Report. Ann Oncol Case Rep. 2025; 5(1): 1027.

cer aggressiveness, the ability to invade normal tissue and to metastasize [2,8-21]. Here we present evidence that supports the hypothesis that because the epithelial derivation of melanocytes would predict that many such malignancies might overexpress VGSCs [17,22], TOL could possibly provide an effective, non-invasive method for treating a case of malignant melanoma that had been characterized by an ulcerated mass with level IV invasion, comprised of a nodular/spindle cell morphology, and measuring 2.1 mm in diameter. The mass was considered to be a stage 3 cancer that typically carries a poor prognosis and even with current established treatment methods, would likely be difficult to treat [23-25], but potentially ideally suited for treatment with TOL.

Case Report

Clinical history: SS is a 51-year-old male with no known risk factors for skin cancer other than frequent, unprotected sun exposure in his youth that was associated with countless sun burns to the point of blistering, who presented with a 5-6-month history of observing a small, painless "bump" that resembled a pimple on the left preauricular region of his face. Fluid could be expressed from the mass, but the bump would eventually return. The slow growth and persistence of the mass indicated to the patient that the mass might be a cyst, but when the skin overlying and surrounding the mass began to turn black, the patient scheduled an appointment with his dermatologist. Physical appearance and clinical experience supported a presumptive diagnosis of malignant melanoma. An excisional biopsy showed histopathological confirmation of a malignant melanoma with at least level IV invasion and up to 2.1 mm of tumor thickness with ulceration. Biopsy margins were positive and the synoptic analysis confirmed a mitotic rate of 2-5/mm^2. Microsatelltosis was absent as was lymphovascular invasion. No neurotropism was seen and tumor regression was absent. Both the peripheral as well as deep margins were involved and pathologic staging was assigned at pT3b. The patient was offered definitive Moh's microsurgical resection with sentinel lymph node sampling which he refused. While seeking other treatment options, he learned about TOL and an Institutional Review Board-approved pilot study that was being conducted at the Global Alliance for Rehabilitative Medicine (GARM) International Foundation Clinic in Roatan, Bay Islands, Honduras. Upon further review of available information describing the conceptual basis and experimental support for developing TOL and the potential benefits and risks associated with treatment, the patient chose to seek additional information about the pilot study and to pursue participation in the study and treatment with TOL.

Preparation, treatment and response: According to the protocol approved by the GARM Clinic, International Foundation Institutional Review Board, an explanation of the rationale and scope of the study was provided and determination of the patient's understanding of the potential risks and benefits of TOL treatment and participation in the study was ascertained. Consent was obtained for harvesting a shave biopsy sample of the preauricular mass (Figure 1A) for histopathologic evaluation to confirm the tissue diagnosis, to provide baseline measurements of tumor morphology, and for immunohistochemical analysis to determine that there was sufficient expression of VGSCs to anticipate a favorable response to treatment with TOL.

For immunohistochemical analysis, sections of the biopsy sample were refrigerated and incubated overnight in a 1:200 dilution of a primary panspecific antibody for VGSCs (Alomone laboratories; www.alomone.com; ASC-003) that recognized a conserved portion of the VGSCs' α-subunit that is found in all isoforms of the sodium channel [26]. After removal from the primary antibody, the sections were rinsed for 3×5 min in phosphate buffered saline and then were incubated for 45 min at room temperature in a 1:1200 dilution of a goat-anti-rabbit secondary antibody conjugated to the Alexa Fluoro-488 fluorophore (Abcam, www.abcam.com; AB-150077). Sections incubated with the secondary antibody alone served as controls for nonspecific labeling. The immunohistochemical reaction revealed a level of VGSC expression depicted in Figure 1B that was considered to be sufficient to anticipate a favorable response to treatment with TOL. The patient was informed of the results obtained from the biopsy and informed consent to proceed with treatment was acquired.

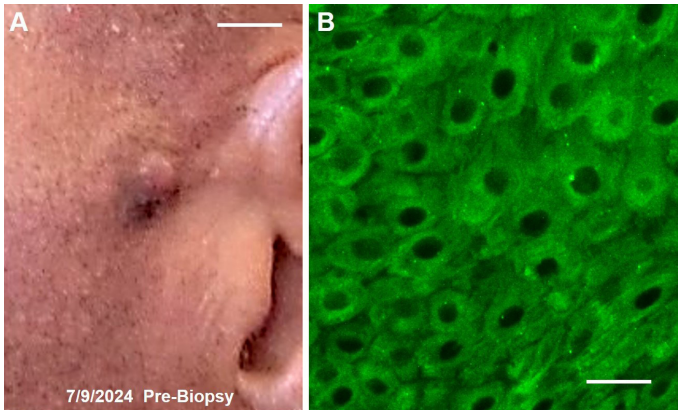

Figure 1: The photograph in A, taken by the patient prior to removing a biopsy sample, depicts the gross appearance of a malignant melanoma located in the left preauricular area of the face. The photomicrograph in B depicts VGSC expression (green label) that was revealed immunohistochemically in a section of a biopsy sample taken from the tumor that was reacted with an anti-body that recognizes a portion of the channels' α-subunit that is conserved in all isoforms of the sodium channel [26]. Calibration bar in A=2.1 mm and in B=25 µm.

Beginning seven days prior to arriving at the clinic, the patient was prescribed and began taking daily doses of oral digoxin (0.25 mg) to achieve a steady-state blood level in the range, 0.50-2.0 ng/ml, which is considered necessary to provide a therapeutic response for treating cardiac disease. No adverse effects were experienced when taking digoxin. A trough level of digoxin was obtained on the morning after the fourth and prior to taking the fifth dose of digoxin to confirm that an appropriate, steady-state level had been achieved. The level was found to be within the target range at 0.9 mcg/L. To maintain steady-state pharmacokinetics for treatment, the 0.25 mg dose of digoxin was administered daily throughout the treatment period that consisted of 2 hours of PEF stimulation administered on 2 successive days, i.e., 1 treatment cycle, weekly for a total of 3 treatment cycles.

On stimulation day 1, the patient's height, weight and vital signs were measured and a baseline electrocardiogram was reviewed by the GARM team. A confirmatory digoxin blood level was obtained before the patient entered the custom-built coaxial ring device (CPEFG) (The Phantom Laboratory, Salem, NY). The patient then entered the CPEFG device and adjusted his position for comfort on an inflatable mattress. The device delivered a uniform pulsed electric field (PEF; 18 V/m, 10 ms positive/negative square wave, 15 ms interstimulus interval) that has been shown to effectively activate VGSCs [27]. Total PEF stimulation time each day was 120 minutes. The appearance of the tumor and closely surrounding area was photographed

by the patient through the cycles of treatment with TOL and is depicted in Figure 2. The patient did not perceive the pulsing of the electric field and did not experience pain or unusual sensory events during or after the first period of stimulation. Similarly, the clinical staff did not observe any issues of concern after the first period of stimulation. In the evening after the second period of stimulation (Figure 2B), the patient did not experience pain, but did notice that the skin overlying and the area around the tumor was sensitive to touch. In the ensuing days, the patient began to notice collections of dried discharge, "puss", in the area on and around the tumor. In the subsequent days prior to and through the second cycle of TOL (Figure 2C & 2D), despite the lack of evidence of surrounding microsatelltosis, the tumor and the area surrounding the primary lesion became progressively inflamed, i.e., erythematous, edemic, and sensitive to the touch, but after the first day of treatment in the third cycle, i.e., fifth period of stimulation (Figure 2E), the signs of inflammation began to diminish and signs of healing were noticed by the day after the completion of the third cycle of TOL (Figure 2G). The healing process continued and was complete within 2 weeks of finishing the treatment with TOL (Figure 3C).

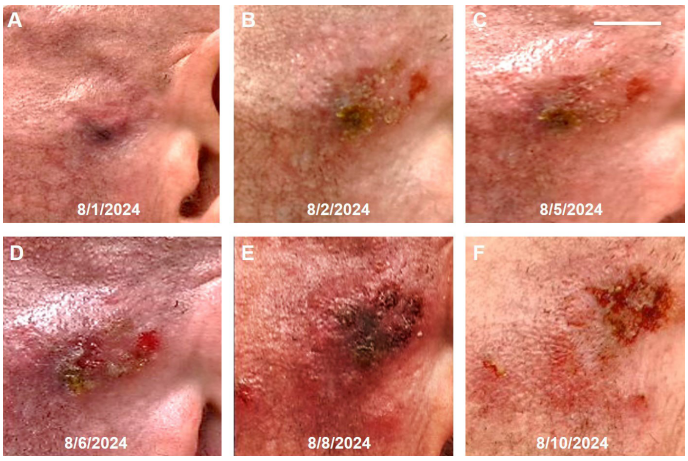

Figure 2: This series of photographs depicts the change in appearance of the melanoma and surrounding skin at progressive stages during the treatment with TOL. The photograph in panel A depicts the appearance of the visible tumor just prior to the patient's first 2 hours in the CPEFG. Panels B and D were taken after the first and second 2-hour period of stimulation. Note the edema **(panels B-D)**, erythema **(panel B)**, and serous leakage **(panels B, D, and E)** that progressively increased during the first 5, 2-hour periods of stimulation. A decrease in edema and serous fluid leakage became evident after the fifth period of stimulation **(panel E)**, and continued to decrease after completion of the stimulation cycles. The photograph in panel F that was taken the day after completion of 3, 2-day cycles of PEF stimulation depicts further reduction of edema, erythema, and serous fluid leakage. Calibration bar in C=2.1 mm.

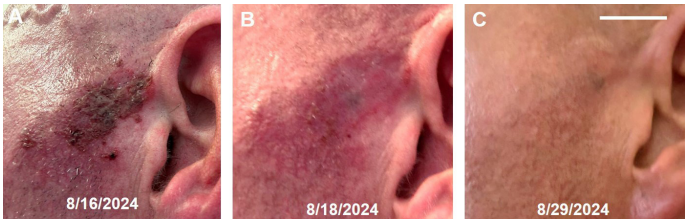

Figure 3: This series of photographs depicts the stages of resolution of the post-treatment crust **(A)** approximately 1-week after completing 3 cycles of treatment with TOL and the resolution of erythema **(panels B and C)** by 3-weeks post-treatment. No residual scarring is apparent. Calibration bar in C=2.1 mm.

Magnetic resonance imaging with and without contrast of the brain and soft tissues of the face and neck depicted in Figure 4 was obtained five weeks after completing treatment with TOL, to assess for evidence of new, residual, stable, recurrent or progressive tumor growth or for any indication of metastatic disease. Sagittal T2 and FLAIR images of the brain, depicted in A and B, revealed areas of hyperintensity in the frontal and parietal periventricular white matter often seen in patients with migraine headache or previous closed head injury. Analysis of T1 sagittal, T1 and T2 axial and coronal images of the face and neck, depicted in C and D, revealed polypoid mucosal changes in the floor of the right maxillary sinus consistent with a history of previous or chronic sinus disease, but were otherwise unremarkable, revealing no evidence of mass effect or abnormal signal intensity consistent with remnants of the previous melanoma or metastatic disease.

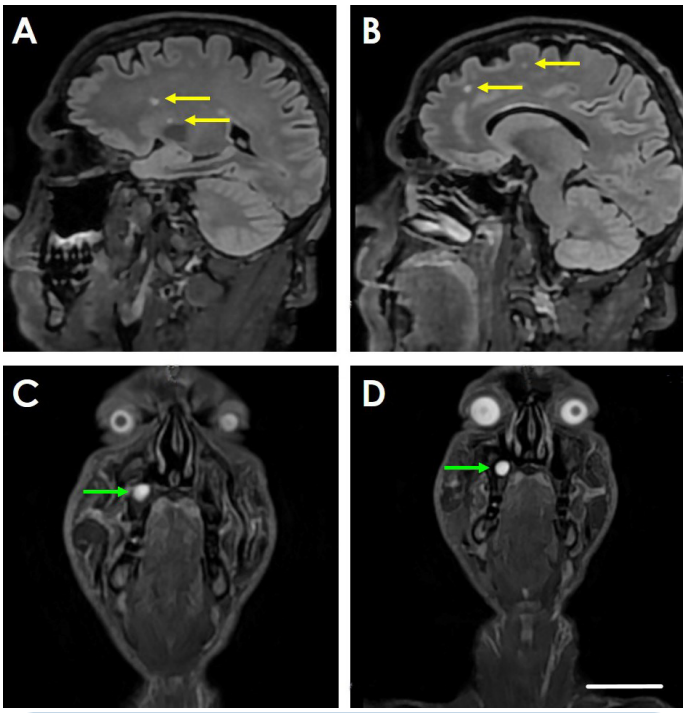

Figure 4: Representative photographs taken of magnetic resonance images generated with and without contrast were obtained to evaluate the results of treatment of a malignant melanoma with TOL, 5 weeks after completing the first round, 3-weekly, 2-day cycles of treatment. The analysis of T2 and FLAIR imaging of the brain in A and B, revealed areas of hyperintensity in the frontal and parietal periventricular white matter (yellow arrows) that are consistent with a history of migraine headache or previous closed head injury. The T1 and T2 axial and coronal images of the face and neck with dotarem contrast shown in C and D revealed polypoid mucosal changes in the floor of the right maxillary sinus (green arrows) that are consistent with a history of previous or chronic sinus disease. No lymphadenopathy was noted and there was no evidence of mass effect or abnormal signal intensity consistent with the previous melanoma or metastatic disease. Calibration bar in D=5 cm.

Discussion

This case report presents evidence that based on the knowledge that melanomas comprise a particularly aggressive group of skin cancers that develop from melanocytic, neural crest cell derivatives of the embryonic ectodermal germ layer, whose cells, when cancerous, frequently over-express VGSCs [4-7], one could predict that malignant melanomas, like other cancers that arise from these epithelial derivatives, are likely to over-express VGSCs [17,22]. If so, similarly to other carcinomas treated

in preclinical studies [4,5], in companion animals [6], and in 2 human patients [7,28], TOL could provide a viable, non-invasive, option for treating malignant melanomas. Consistent with the results of earlier reports and on-going pilot studies, treatment with TOL has been found to be safe, well-tolerated, and effective in eliminating or reducing the tumor size and growth without damaging surrounding normal tissue or leaving a residual, undesired, debilitating, or potentially deforming scar [28] that can accompany standard and effective surgical, radiological, chemical, and immune mediated treatments especially when administered in late stage disease (Figure 5) [2,24,25].

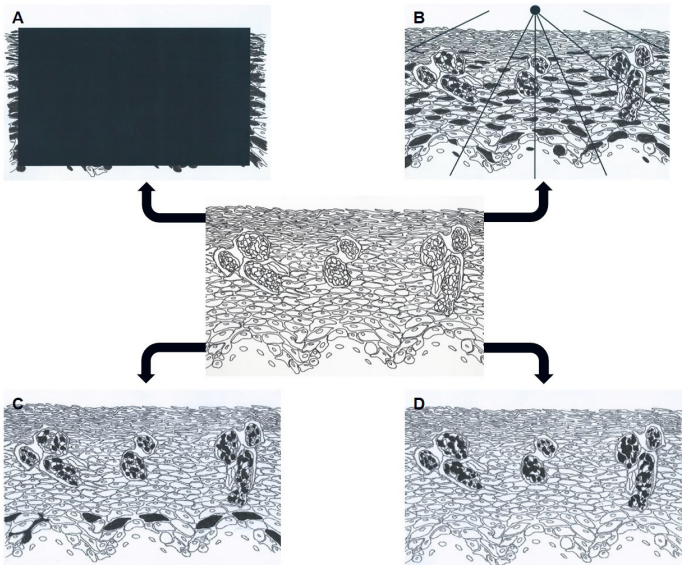

Figure 5: The diagram in the center illustrates a representative section of skin that contains nests of atypical melanocytes that extend from the stratum basale to the stratum lucidum prior to treatment. The areas shaded in black and profiles filled with black represent cells that have been damaged by forms of treatment that will undergo variable degrees of inflammation and healing that often produce pain, in order to protect and isolate the injured tissue, edema, heat, and erythema to remove debris and provide restorative oxygen and nutrients to surviving tissues in and around the site of injury. Panels A-D depict how different methods of treatment may affect disease control and healing. Panel A depicts the complete surgical removal of active cancer cells and supportive normal tissue with a non-cancerous margin. This method is potentially curative but depending on the size, location, and complexity of tumor invasion is prone to leaving a significant disfiguring scar. Panel B depicts the potentially curative destruction elimination of active cancer cells using radiation therapy. Depending on the proximity to the active cancer cells, both abnormal and surrounding normal abnormal cells in the path of the radiation are subject to lethal, ionizing radiation that can eliminate the cancer but carries a risk of extensive scarring and the initiation of neoplastic change. Panel C depicts chemo- and immune therapies that when administered early in the course of disease have slowed neoplastic growth and replication, increased overall survival and variably decreased the incidence of undesirable adverse effects. Despite advances in the selectivity of current targeted therapies, off-target effects still occur that compromise the function of normal tissue, e.g., stratum germinativum or stratum basale (regenerative layer of skin), and potentially survival of the host. Panel D depicts the effect of treatment with TOL that destroys cancer cells that over-express VGSCs leaving normal cells the surrounding tissues unharmed and thereby precluding scar formation.

The implementation of educational programs that emphasize the importance of physical features, such as blonde or red hair, blue or green eye color, freckles, a fair complexion and sensitivity to sun exposure that place individuals at increased risk for skin cancer and the modification of patient-controlled behaviors such as limiting extended periods of mid-day sun exposure, utilization of protective apparel, the use of topical sunscreens, performing frequent self-examination, and regular dermatologic evaluations, has reduced the risk of developing melanoma and increased the likelihood of early detection when they occur. Consequently, overall 5-year survival has increased, standard treatment options are more effective, and the severity of adverse effects attributed to off-target tissue damage or functional manipulation of normal tissues, e.g., pain, scarring and disfigurement as well as affecting cardiovascular, pulmonary and gastrointestinal function [25], are minimal. Because of the benefits realized when using the current standard of care, TOL is less likely to receive serious consideration as a potential option for malignant melanomas when discovered at an early stage. That said, the phenotypic and genetic complexity that characterize malignant melanomas continues to thwart efforts at early diagnosis, thus pre-empting the potential effectiveness and tolerance hoped for when standard treatments are used to treat late stage disease and encourages further study to develop alternative methods, like TOL, that may be more effective, better tolerated, and be associated with fewer long-term, undesirable features (Figure 5) when used to treat disease that is discovered at a late stage [2,21,28].

The observation that TOL was found to be beneficial for treating yet another form of malignancy further supports the hypothesis that because the VGSC and Na^+, K^+-ATPase mechanism plays a dynamic role [4-7] both to ensure cell survival through the generation and maintenance of the ionic transmembrane potential difference that supports intercellular communication and cellular homeostasis in normal and malignant cells, and when over-expressed in cancer cells enhances the ability to invade normal tissue and to metastasize [2,8-21], is essential and conserved throughout the animal kingdom, unlike treatments based on manipulating unique and highly specific mechanisms, is likely to benefit a broad range of conditions in a wide range of species and is reasonable to anticipate that TOL may offer a viable option to consider as part of the algorithm for treating many forms of advanced carcinoma.

Although recent dermatologic evaluation, 6 months after beginning treatment with TOL, has revealed no evidence of new or residual tumor, or physical signs warranting the need for additional imaging, the results, while promising at this time, will require further observation to determine whether and for how long the resolution of disease or the benefit of treatment will be maintained and additional studies to establish that the therapeutic response observed here is consistent. Regardless, the results detailed in this report clearly indicate that TOL warrants further study to determine where and when in the therapeutic algorithm TOL might produce the most beneficial response and when it should be considered when treating cancers that over-express VGSC and Na^+, K^+-ATPase.

Author declarations

Acknowledgments

The authors wish to thank Paige Miller, Hank Mills, Heather Terry, Keyon Janani, Fluvia Humphreys, M.D., Agustin Jiminez, M.D., Gavin Simoneaux, and Mayra Hoch for their timely efforts

in coordinating patient scheduling, troubleshooting protocol for efficiency, and record organization and Harris Blackman, M.D., West Jefferson Medical Center, Metairie, LA for providing insight and expertise from the perspective of a practicing dermatologist.

Patents

A patent for the technology described in this manuscript entitled, Targeted Osmotic Lysis of Cancer Cells – File No. 11M01 (Serial No. 13/552,909) Paul DJ and Gould HJ III was allowed on 12/30/2014.

Funding

This research was funded by a research services contract from Oleander Medical Technologies, Inc. to DP and HJG.

Conflicts of interest

D.P., H.J.G. and spouse, Paige R. Miller, are co-founders and managing members of Oleander Medical Technologies, Inc.

Ethics statement

Institutional Review Board Statement**:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the GARM International Foundation Institutional Review Board, GARM #12132023 - Targeted Osmotic Lysis in Advanced Carcinoma: A Patient Pilot Study, approval date - 12/14/2023.

Author contributions

Conceptualization, Dennis Paul and Harry J. Gould, III; Data curation, Rajiv S. Dahiya, and Harry J. Gould, III; Formal analysis, Rajiv Dahiya and Harry J. Gould, III; Investigation, Rajiv S. Dahiya and Harry J. Gould, III; Methodology, Rajiv S. Dahiya, Dennis Paul, and Harry J. Gould, III; Supervision, Rajiv S. Dahiya, Dennis Paul, and Harry J. Gould, III; Validation, Rajiv S. Dahiya and Harry J. Gould, III; Visualization, Harry J. Gould, III; Immunohistofluorescence of VGSCs, Abigail Sims; Writing – original draft, Harry J. Gould, III and Rajiv S. Dahiya; Writing – review & editing, Rajiv S. Dahiya, Dennis Paul, and Harry J. Gould, III.

Data availability statement

The data presented in this study are available on request from the corresponding author.

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