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 ORIGINAL ARTICLE

Comparing the Safety and Effectiveness of Microfocused Ultrasound: Standard Versus Targeted Tissue Protocol in Lifting and Tightening the Lower Face and Upper Neck

Emily Wood MD,[a] Alexes Gonzalez BS MS,[b] Rawaa Almukhtar MD MPH,[c] Leysin Fletcher PA-C,[b] Sabrina Fabi MD[b,d]

[a]Westlake Dermatology, Austin, TX
[b]Cosmetic Laser Dermatology: A West Dermatology Company, San Diego, CA
[c]Laser & Cosmetic Dermatology, Scripps Health, San Diego, CA
[d]University of California, San Diego – Department of Dermatology, San Diego, CA

ABSTRACT

Background: Micro-focused ultrasound with visualization (MFU-V) delivers energy to specific soft tissue layers beneath the epidermis with the ability to lift and tighten the lower face and neck.
Objective: To determine the efficacy of microfocused ultrasound with visualization (MFU-V) using a standard treatment line protocol versus a customized treatment line protocol based on the patient's unique anatomy targeting the superficial muscular aponeurotic system and fibrous septae for lifting and tightening of the lower face and neck
Methods: This was a single center, prospective, randomized, investigator blinded clinical trial. 51 subjects were randomized to receive a single treatment of MFU-V targeting the lower face and neck using either a standard or custom treatment protocol.
Results: Subjects in both standard and custom treatment groups noted a greater than one point improvement in jawline laxity. Three-dimensional photography measurements also demonstrated lifting of the lower face and neck in both treatment groups.
Conclusion: Custom and standard treatment MFU-V protocols produce a safe and effective treatment for tightening and lifting the lower face and neck. Custom treatment protocols aid in maximizing results for patients with variations in the anatomy of the lower face and neck.

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INTRODUCTION

A well contoured jawline is a key factor in the perception of facial attractiveness and youthfulness in both men and women.[1-3] Patients are increasingly interested in non-invasive methods with little to no downtime to improve jowling and sagging of the lower face and neck. These changes are caused by loss of bone, subcutaneous fat repositioning, loosening of facial ligaments, and a decrease in collagen and elastin fibers within the dermis and subcutis.[4] Microfocused ultrasound with visualization system (MFU-V) (Ulthera Inc., Ultherapy®, Merz North America, Inc., Raleigh, NC) delivers ultrasound energy below the epidermis creating precise 1 mm^3 microthermal lesions at approximately 65°C in specific anatomical layers of the skin including the dermis at 1.5 mm of depth, deep dermis at 3.0 mm of depth and the sub-dermal plane including the superficial musculo-aponeurotic system (SMAS) and fibrous septae at 4.5 mm.[5,6] MFU-V has the ability to bypass the epidermis, therefore; eliminating the downtime created by many non-ablative and ablative devices used for neocollagensis.[7] MFU-V is based on principles of wound healing to produce robust neocollagenesis which creates lifting and tightening of the treated tissue.

Treating all patients with a one size fits all standard protocol does not take into consideration variances in facial anatomy and skin tissue thickness and may result in suboptimal results and poor patient satisfaction.[8] Customizing the dual depth treatment protocol to the anatomy of each patient by visualizing the superficial muscular aponeurotic system (SMAS) and fibrous septae of the lower face and upper neck, which in some subjects can be found at 4.5 mm deep and in others at 3.0 mm deep, and then selecting the appropriate depth transducers

may result in a more efficacious treatment with higher patient satisfaction as all coagulation point placement is being optimized.[9]

MATERIALS AND METHODS

This was a single center, prospective, randomized, investigator blinded clinical trial. Institutional review board approval was obtained to ensure the study was conducted in accordance with the Declaration of Helinski and the International Conference on Harmonization. After obtaining informed consent, 51 female subjects were enrolled in the trial, with a median age of 55, and Fitzpatrick skin types II-V. Subjects had moderate to severe sagging of the jawline area (grade II-III on the Merz Jawline Assessment Scale). Subjects were excluded if they were pregnant, breastfeeding, or planning pregnancy for the duration of the trial. Additionally, subjects were excluded if they were using any opioids for pain control. Exclusions also included the presence of active or local systemic skin disease that may affect wound healing, history of Bell's palsy, significant scarring in the area, open wounds, severe or cystic acne in the treatment area, active implants (pacemakers or defibrillators) or metallic implants in the area (dental implants not included). History of microdermabrasion or glycolic acid peel to the treatment area within two weeks prior to study participation. History of any energy based device procedure for skin tightening within the past 12 months, injectable filler of any type in the treatment area within the past 24 months, neurotoxin treatment in the area within the past six months, fractional and fully ablative resurfacing laser treatment within the past 6 months, surgical dermabrasion or deep facial peels within the past 6 months, history of facelifts, neck surgery within the past two years, any history of deoxycholic acid or cryotherapy to the treatment area, history of contour threads in the past year or initiation of retinoids 14 days prior to the start of the study, use of antiplatelet/anticoaugulants, systemic immunosuppressants, and/or autoimmune connective tissue disease.

Subjects were randomized to receive 1 MFU-V treatment of the lower face and upper neck utilizing either the standard or custom dual depth treatment protocol. The standard treatment protocol included 360 lines with the 4.5 mm transducer followed by 310 lines with the 3.0 mm transducer, both at the default energy level setting of 2. The custom dual depth treatment protocol was based on the patient's unique anatomical depth of the SMAS of the lower face and the platysma of the upper neck using visualization on the device. 360 lines were delivered with either the 4.5 mm or the 3.0 mm transducer, depending on the depth of the SMAS and platysma followed by 310 lines with the 3.0 mm depth transducer, or the 1.5 mm transducer depending on the depth of the fibrous septae. Prior to treatment, subjects were offered oral pre-medication of 5-10 mg of diazepam, 800 mg of ibuprofen, and/or 1 gram of acetaminophen. Immediately post treatment, subjects were asked to rate their level of discomfort during treatment using a 10-point visual pain scale (0= no pain, 10= worst pain). Subjects returned for follow up visits at month 3 and month 6 for evaluations. Vectra 3D photographs (Canfield Scientific Inc., Parsippany, New Jersey) were taken at baseline, month 3, and month 6. 3D photographs were then analyzed with Mirror Photofile Software (Canfield Scientific Inc., Parsippany, NJ) to measure submental lift. The following evaluations were also conducted: Blinded Evaluator Merz Jawline scale (0= no sagging, 1= mild sagging, 2= moderate sagging, 3= severe sagging, 4= very severe sagging; Figure 1) at day 0, month 3 and month 6; and Investigator Global Aesthetic Improvement Scale (I-GAIS) (1= Very Much Improved, 2= Much Improved, 3= Improved, 4= No change, 5= Worse), Subject Global Aesthetic Improvement Scale (S-GAIS) (1= Very Much Improved, 2= Much Improved, 3= Improved, 4= No change, 5= Worse) and Subject Satisfaction Questionnaire (0= Completely Dissatisfied, 1= Moderately Dissatisfied, 3= Neither Dissatisfied Nor Satisfied, 4= Mildly Satisfied, 5= Moderately Satisfied, 6= Completely Satisfied), were conducted at month 3 and month 6. Any adverse events were recorded.

Statistical Analyses

All statistical tests were two-sided and interpreted at a 5% significance level. Descriptive statistics (ie, mean standard deviation, etc) were provided for all continuous variables and frequencies for all categorical variables. In order to track changes for individual variables across all relevant visits, single-

FIGURE 1. Merz Jawline Scale (0=no sagging, 1=mild sagging, 2=moderate sagging, 3=severe sagging, 4=very severe sagging).

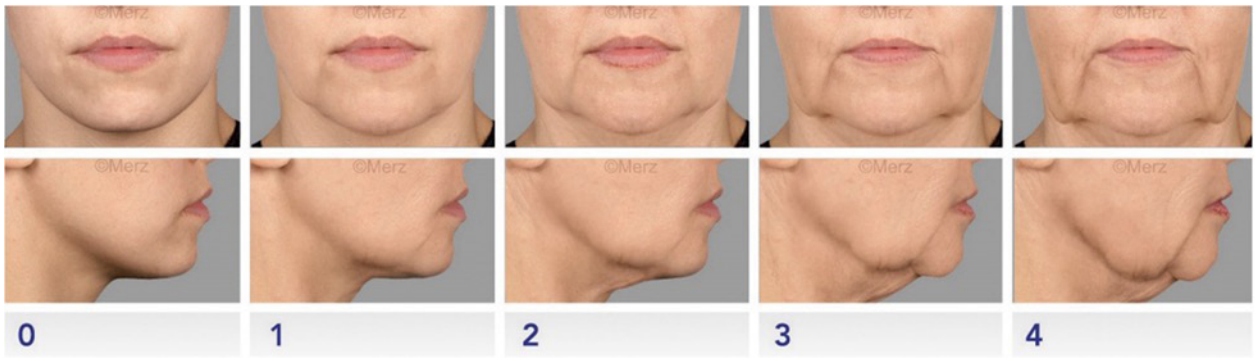
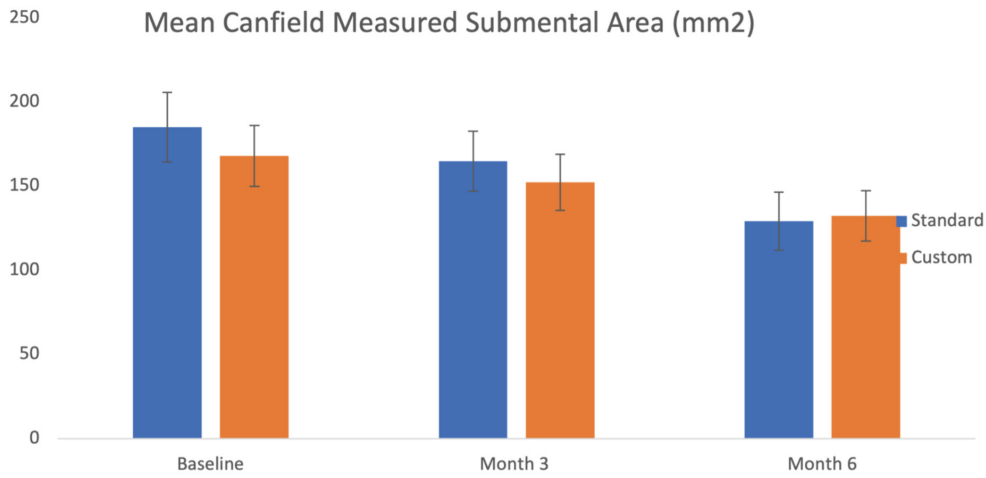


TABLE 1.

Both Standard and Custom Groups Demonstrated Improvement in Submental Lift as Measured by 3D Photography



factor Analysis of Variance (ANOVA) tests were used, while comparisons between two individual visits were done using two sample t-tests assuming equal variance. *P*-values < 0.05 were considered clinically significant.

RESULTS

Forty-one subjects completed the trial, Fitzpatrick II-V skin types, with a mean age of 55 (37 to 65 years old). Nineteen subjects were randomized to the standard treatment group and 22 subjects were randomized to the custom treatment group. Of the subjects randomized to the custom treatment group, 13 subjects still had platysma identified at 4.5 mm and were treated with the 4.5 mm and 3.0 mm depth transducers. 9 subjects had a more superficial platysma at 3.0 mm and were treated with the 3.0 mm and 1.5 mm depth transducers. Seven subjects were lost to follow up and three subjects withdrew consent, as this study took place during the COVID-19 pandemic.

Primary Endpoint

Standard and custom treatment groups both demonstrated improvement with regards to the degree of submental lift as measured by 3D photography (Table 1, Figures 2-4). No statistical significance was noted between groups with regards to submental lift. The mean submental area for the standard group was 185.083 mm^2 ± 101.44 at baseline decreasing to 164.78 mm^2 ± 85.11 at month 3 with further reduction at month 6, 129.11 mm^2 ± 75.06. For the custom group, the mean submental area at baseline was less at 167.85 mm^2 ± 87.20. Reduction in mean submental area was also seen in the custom group with month 3 mean submental area of 152.6 mm^2 ± 80.34 and month 6 being 132.28 mm^2 ± 68.56,

The mean submental lift was 23.28 mm^2 ± 74. 31 at month 3 and 55.52 mm^2 ± 80.60 at month 6 for the standard treatment group.

FIGURE 2. Forty-nine-year-old woman treated with 4.5 mm and 3.0 mm transducers demonstrating a 63% reduction in submental area from baseline to day 180.

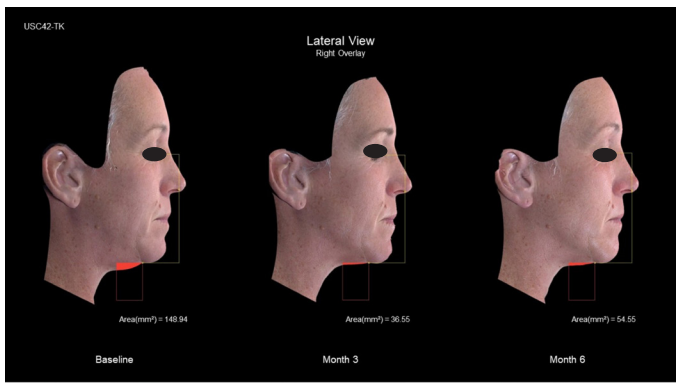


FIGURE 3. Fifty-nine-year-old woman treated with 4.5 mm and 3.0 mm transducers demonstrating a 57% reduction in submental area from baseline to day 180.

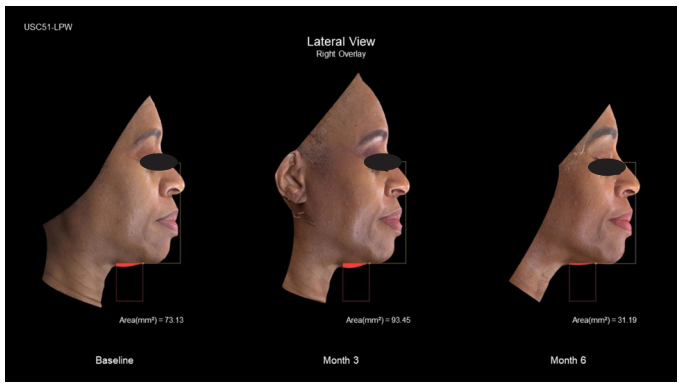


FIGURE 4. Fifty-two-year-old woman treated with 3.0 mm and 1.5 mm transducers demonstrating a 38% reduction in submental area from baseline to day 180.

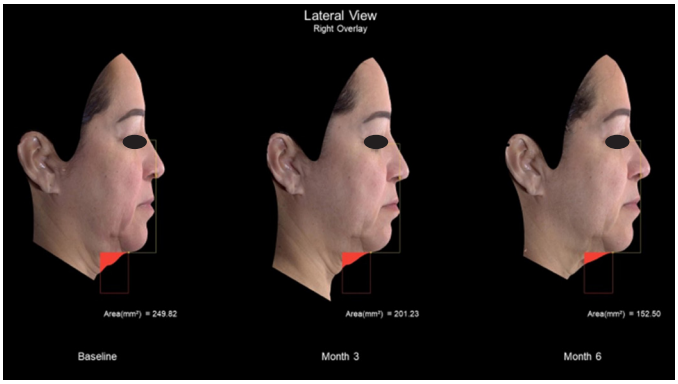
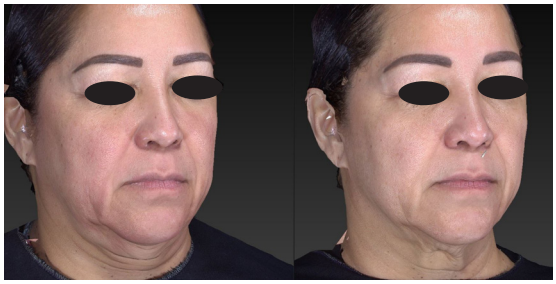


FIGURE 5. Forty-nine-year-old woman 6 months post one standard MFU-V treatment to the lower face and upper neck 4.5 mm and 3.0 mm transducers.

FIGURE 6. Fifty-nine-year-old woman 6 months post one custom MFU-V treatment to the lower face and neck utilizing the 4.5 mm and 3.0 mm transducers.

FIGURE 7. Fifty-two-year-old woman 6 months post one custom MFU-V treatment to the lower face and neck utilizing the 3.0 mm and 1.5 mm transducers.



The mean submental lift was 15.69 mm^2 ± 49.60 at month 3 and 36.15 mm^2 ± 58.10 at month 6 for the custom treatment group.

The mean percent change in submental lift from baseline to month 3 was 11.33% and 9.20%, in standard and custom groups respectively (Table 2). The mean percent submental lift from baseline to month 6 was 28.86% and 20.80% for standard and custom treatment groups, respectively.

Secondary Endpoints

Both standard and custom group treated subjects showed a statistically significant improvement in jawline laxity according to the Blinded Evaluator Merz Jawline Scale from screening to month 6 (P<0.01, Single Factor ANOVA; Table 3, Figures 5-7). The Merz jawline scale at baseline to month 6 for the standard group was 2.38 ± 0.58 and 1.42 ± 0.77, respectively. The Merz jawline scale for baseline to month 6 for the custom group was 2.56 ± 0.50 and 1.45 ± 0.86, respectively. The standard group showed a 0.95 change on the Merz Jawline 5-point scale at month 6, and the custom group showed a 1.11 change on the Merz Jawline 5-point scale at month 6. Seventy-four percent of subjects in the standard group and 77% of subjects in the custom group had a ±1-point improvement in jawline laxity at month 6 according to the Merz Jawline Scale.

At month 6, the custom group showed a statistically significant improved mean I-GAIS than those in the standard group, (P=0.01, two-sample t-test; Figure 5). At month 6, the standard group mean I-GAIS was 2.68 ± 1.20 ("improved") and the custom group mean I-GAIS was 1.77 ±1.02 ("much improved").

There was no statistically significant difference between S-GAIS in standard and custom treatment groups. Overall, the majority of subjects in both groups noted their GAIS was "much improved". The mean S-GAIS at month 6 for the standard group was 2.16 ± 0.96 and the custom group was 1.82 ± 0.96.

At month 3 and month 6, subject satisfaction scores for both groups were positive. At month 3, subject satisfaction scores were 4.56 ± 1.47 and 4.75 ± 1. for standard and custom groups, respectively, with both groups moderately satisfied with their results. At month 6, subject satisfaction scores were 5.05 ± 1.08 and 5.04 ± 1.50, respectively, with both groups moderately satisfied with their results.

Both standard and custom groups rated the pain during treatment similarly, with the standard group rating a 6.16 ± 1.25 and the custom group rating a 6.24 ± 1.53. There were no adverse events.

DISCUSSION

It is well known that a combination of 4.5 mm and 3.0 mm transducers causes a significant lift of the skin underneath the submentum.10-13 Oni and colleagues saw an average submental lift of 45.2 mm^2 delivering 295 lines in the lower

TABLE 2.

Percent Change in Submental Measurement From Baseline to Month 3 and Baseline to Month 6 in Standard and Custom Treatment Groups. A negative percent change indicates increased submental lift.

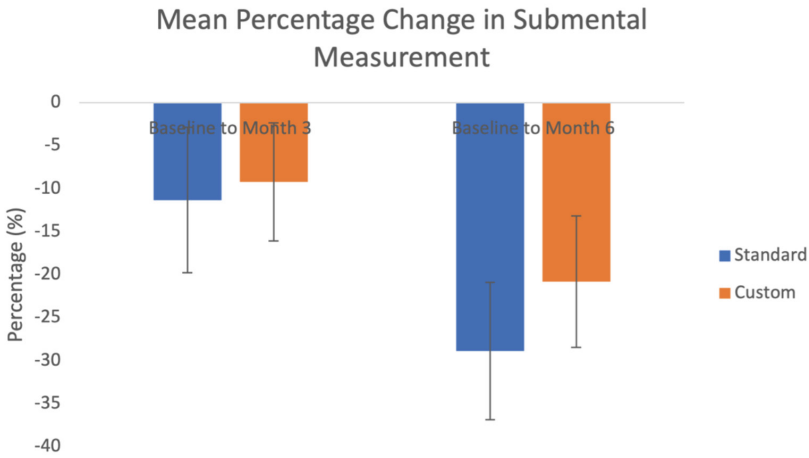
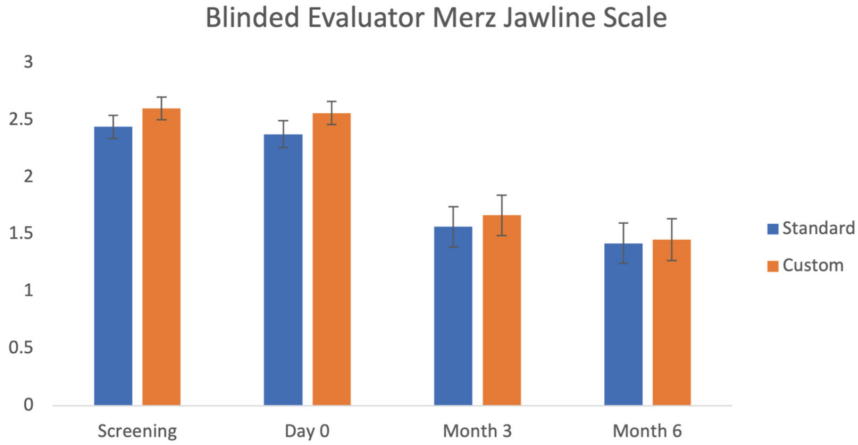


TABLE 3.

A Statistically Significant 1 Point Improvement in Jawline Laxity was Noted in Both Groups From Screening To Month 6, (*P*<0.01, Single Factor ANOVA)



face and neck with the 4.5 and 3.0 mm depth transducers.[13] Our results demonstrate that when the SMAS and platysma are found and targeted at a more superficial depth of 3.0 mm, and then followed by treatment with a 1.5 depth transducer, we can produce a submental lift that is noninferior to patients receiving the standard treatment protocol using the 4.5 mm and 3.0 mm depth transducers. In this study, we found that of the 22 subjects randomized to the custom arm, 41 % of the time (n = 9), their platysma and SMAS were found to be more superficial at 3.0 mm.

In order to provide a more thorough evaluation of the degree of lift produced by MFU-V, 3D images were taken to measure the reduction in submental area. Oni and colleagues' previous study evaluating MFU-V for submental lift utilized a reduction of >20 mm^2 to indicate a quantitative improvement in submental laxity that translates to visible clinical improvement.[13] Both treatment groups in our trial showed robust submental lift according to prior standardized metrics of improvement with a mean lift of 55.52 mm^2 ± 80.60 from baseline to month 6 for the standard group and 36.15 mm^2 ± 58.10 from baseline to month 6 for the custom treatment group. Our evaluation of submental lift from both a quantitative and qualitative perspective ensures measurement of device efficacy translates to real world improvement in order to produce high patient satisfaction.[14,15]

We saw a statistically significant 1-point improvement in jawline contour using the Merz Jawline Scale in both standard and custom treatment groups, an endpoint that has never been evaluated in prior MFU-V studies. Our study demonstrates

comparable improvement in jawline contour when compared with calcium hydroxylapatite and hyaluronic acid filler for jawline augmentation. Moradi and colleagues' recent study evaluating the effectiveness and safety of calcium hydroxylapatite with lidocaine for improving jawline contour defined treatment response as a ≥1-point improvement in jawline contour according the Merz jawline scale, with a treatment response rate of 75.6% for the treatment group and 8.8% for the control group at week 12.[16] Green and colleagues recent pivotal study evaluating VYC-25L for jawline contour demonstrated ≥1 improvement at 6 months in jawline contour in 68.5% of subjects according to the Allergan Loss of Jawline Definition Scale.[17] Our results showing at least a 1-point improvement in jawline contour indicate clinically relevant results as it is a standard metric used for aesthetic medicine clinical trials to indicate meaningful improvement.[16,18-22]

The I-GAIS at month 6 was statistically significant for greater improvement for the custom group compared with the standard group. Possible reasons for the slightly greater improvement noted by the blinded investigator at month 6 may be due to differences in BMI among standard and custom treatment groups. BMI of subjects was not recorded in our study; however, in Oni and colleagues' study evaluating MFU-V for skin laxity and tightening of the lower face, reviewer assessed global aesthetic improvement increased when 11 of the 93 subjects were excluded from data analysis due to having a BMI >30 kg/m^2.[13] We do know that those of lower BMI, who are greater than 40, have SMAS and platysma at more superficial planes, such as 3.0 mm based on ultrasound imaging in 150 live patients performed by Casabona and colleagues.[9,23] Perhaps those in the custom treatment group demonstrated slightly better I-GAIS due to having a lower BMI which may equivocate to their SMAS/platysma and fibrous septae being located at a more superficial depth. Future studies with a larger sample size could increase the power of our study.

Importantly, S-GAIS and subject satisfaction scores for both treatment groups indicated the majority of patients appreciated a high degree of improvement in the appearance of their lower face and neck. Both standard and custom protocol treatments were well tolerated, and no adverse events occurred.

The seven subjects who were lost to follow up occurred during the COVID-19 lockdowns. The three subjects who withdrew consent were due to compliance related issues. One subject was excluded from three-dimensional data analysis due to poor positioning during photography.

CONCLUSION

This trial emphasizes the importance of visualization with ultrasound to confirm all coagulation points are delivered, so optimal energy gets transferred to tissue and to create a custom treatment protocol for the patient's unique anatomy to maximize results and patient satisfaction. MFU-V is a powerful tool to significantly improve jawline contour which is crucial for optimizing dynamic three-dimensional facial rejuvenation.

DISCLOSURES

This study was funded by Merz North America Inc. Dr Sabrina Fabi is an investigator and consultant for Merz North America Inc. The other authors have no additional relevant disclosures.

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AUTHOR CORRESPONDENCE

Emily Wood MD
E-mail:..... drwood@westlakedermatology.com