FACIAL SKIN TIGHTENING WITH MICROFOCUSED ULTRASOUND AND DERMAL FILLERS: CONSIDERATIONS FOR PATIENT SELECTION AND OUTCOMES

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Statement of Need

Human facial aging is a gradual and ongoing process involving various factors including photodamage, skin laxity, volume loss of subcutaneous tissue, and bony resorption. As the aging US population is growing, minimally invasive strategies have become the primary treatment modalities for addressing mild to moderate age-related facial changes. The introduction of microfocused ultrasound (MFU) represents a method to produce a deeper wound healing response with increased collagen remodeling and more durable clinical response. MFU-V treatment protocols continue to be refined and use in combination with other minimally invasive strategies including injectable dermal fillers such as diluted calcium hydroxylapatite for skin laxity and appearance of lines in the neck and décolletage has been studied. Need exists for expanded understanding of dermatology providers on the application of microfocused ultrasound in combination with injectable dermal fillers as a treatment approach for lifting skin on the neck and face and for improving lines and wrinkles on the chest.

Educational Objectives

The information and educational goals for this enduring activity are to expand awareness of microfocused ultrasound as an emerging treatment strategy for the effects of normal facial aging and to demonstrate positive outcomes in facial skin tightening strategies utilizing combination treatment including microfocused ultrasound and injectable dermal fillers. Upon completion of this continuing education activity participants should be able to:

- Summarize the mechanism of action of high-resolution ultrasound imaging (MFU-V) for lifting skin on the neck and face, improving lines and wrinkles on the chest and improving collagen synthesis
- Identify patients best suited for treatment with MFU-V in combination with injectable dermal fillers
- Compare features, benefits, and safety profile MFU-V treatment in lifting skin on the neck and face and for improving lines and wrinkles on the chest

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants, nurse practitioners, and other healthcare providers with an interest in aesthetic treatment of patients of all skin types.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Facial Skin Tightening With Microfocused Ultrasound and Dermal Fillers: Considerations for Patient Selection and Outcomes

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ABSTRACT

Introduction: Microfocused ultrasound (MFU) is a heat technology that is developed from focused ultrasound (FU) used in a high intense mode to generate heat (HIFU). Patient assessment is very complex and involves more than just addressing complaints. It is a challenge to evaluate, decide on options, and give treatments that guarantee the best outcomes. In order to facilitate the process, the authors divided the protocol into five steps: Assess (expectations, features); Decide (which depth to customize); Select (choose a number of lines to achieve the objective); Plan (combination, if needed); Treat (documentation, safety, and comfort).

Methods: The PubMed search engine was used to search all publications from 1900–2019 that mention HIFU. The information collected was then grouped into the five protocol steps.

Discussion: MFU is a focused ultrasound device that, at certain energy levels, produces heat over 55ºC at the focal point, which leads to thermal coagulation points (TCPs) in the target tissue. The creation of TCPs leads to a healing cascade, ending with neocollagenesis and neoelastogenesis. At different levels, this can bring about either a lifting effect or skin tightening, depending on the structure targeted. Therefore, the two most important tools for precision and efficacy of treatment are visualization with ultrasound and real-time evaluation of severity and structural changes (such as bone or fat loss).

Conclusion: MFU-V is a well-known and, based on the evidence, an effective tool for non-invasive lifting and skin tightening. The secret to successful use of the device is to assess adequately patient needs and expectations and plan ahead for the combination of other treatment if necessary to achieve the desired outcome.

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BACKGROUND

Microfocused ultrasound (MFU) is a technology developed from focused ultrasound (FU) and used in high intensity mode to generate heat (high intensity focused ultrasound; HIFU). Focused ultrasound was discovered by Frank Fry in 1972 and was used to destroy brain cancer cells.[1] HIFU is a modality in which the ultrasound beam is focused precisely on the target to deliver acoustic energy to part of the body in a non-invasive or minimally invasive manner. The purpose of HIFU is to heat a target tissue without affecting the tissue in the ultrasound propagation pathway. HIFU can increase the temperature of a selected area above 55ºC, which results in coagulative necrosis and immediate cell death in a specific depth through a focused ultrasound beam.

Because the ultrasound wavelength at megahertz frequencies has a millimeter-scale beam size and the ultrasound probe has a concave shape, the ultrasound beam can be focused into small, clinically relevant volumes of tissue. The energy absorption raises the temperature at the focus point but increases only to non-cytotoxic levels outside the region.[2,3] Almost 30 years later, noninvasive facial treatment with intense microfocused ultrasound (MFU) started to be developed, such as Ulthera® System (Merz North America, Raleigh, NC), which also includes ultrasound visualization (DeepSee®; Merz North America, Raleigh, NC), followed by Doblo (Hironic®, Korea), which does not include real-time visualization in some models, and Ultraformer (Cryomed®, Australia), which does not offer visualization (Table1).

During development, some HIFU parameters were adjusted to reach the goal of generating thermal coagulation zones (TCPs). The final prototype transducer had shorter pulse durations of 50–200ms, a higher frequency of 4 to 7 MHz, and a decreased energy of 0.5 to 10J.[4] As a result, more precise energy delivery was achieved with the microfocused ultrasound with visualization (MFU-V) device during aesthetic treatments for facial tissue.

In 2004, the first preclinical trials were started with a prototype device, followed shortly thereafter by several clinical trials.[5-8] White and colleagues[6] reported the first aesthetic use of focused ultrasonography and its ability to specifically target the

TABLE 1.

HIFU Devices, Transducers, and Visualization Method				
Device	**Brand**	**Approved**	**Visualization**	**Transducers**
Ultherapy - MFU	Merz Pharma - Germany	Canada, US, Europe, Asia, Australia, Central and South America	Real Time USG	1,5mm(micro) 3.0mm (micro) 4,5mm (micro)
Doublo - HIFU	Hironic - Korea	Asia, South America	Not Real Time USG in some versions	1,5mm (micro) 3,0mm (micro) 4,5mm (micro) 13mm (macro)
Ultraformer - HIFU	Cryomed - Australia	US, Europe, South America, China, Russia, Australia	No Visualization	1,5mm (micro) 2,0mm (micro) 3,0mm (micro) 4,5mm (micro) 6,0mm (macro) 9,0mm (macro) 13,0mm (macro)

superficial muscular aponeurotic system (SMAS). The current clearance by the FDA for the aesthetic use of MFU-V are brow-lift, face, and neck lift, and décolleté tightening.[9-12]

METHODS

The PubMed search engine was used to review all publications from 1900–2019 that mention high intensity focused ultrasound, and the information collected was collated into a step by step approach for didactic purposes.

Mechanism of Action

As MFU is a focused ultrasound device, at certain energy levels, it produces heat over 55ºC at the focal point, which leads to thermal coagulation points (TCPs) in the target tissue. The creation of TCPs leads to a healing cascade, ending with neocollagenesis and neoelastogenesis. This healing is regulated and described as an "orchestra playing" by Reinke and Song,[14] which begins immediately after the first phase of the injury and lasts for 1 to 3 days. This is the most important phase for the purpose of collagen stimulation.[15,16] During this very early phase, mediators such as interleukins (IL-1 and IL-6), tumoral necrosis factor (TNF-α), and other factors (FGF-2, IGF-1, TGF-β, and VEGF) lead to the production of new collagen and elastin, as well as neovascularization within the extra cellular matrix (ECM).

The second phase of proliferation lasts for 5-10 days. Under the control of regulating cytokines (IFN-α, TGF-β), fibroblasts synthesize collagen, fibronectin, and other basic substances needed for wound healing. These represent the basis for the new connective tissue matrix, serving to close tissue gaps and to restore the mechanical strength of the wound. Subsequently, the synthesis of collagen increases throughout the wound, while the proliferation of fibroblasts declines successively, adjusting to a balance between synthesis and degradation of the ECM.[17] The third phase can last from 21 days to 1 year, depending on the scar tissue.

One of the most important factors is sufficient stimulation during the first phase to have enough fibroblasts to produce organized collagen and elastin. Organized collagen formation (scar tissue) is the physiological endpoint of mammalian wound repair. There is some evidence that inflammation during the process of wound healing is directly linked to the extent of scar formation.[15] First, fetal wound healing, which lacks the typical inflammatory response, is scarless until a certain age.[18,19] In addition, scar formation does occur when inflammation is induced in fetal wounds.[20] Also, reproductive hormones have been shown to have an influence on inflammation and the formation of scars. Studies show that low estrogen levels in mice resulted in an impaired rate of healing with excessive inflammation and scarring.[15,21,22]

To summarize, a TCP induces tissue coagulation and necrosis and starts the healing cascade. To achieve the desired quantity and quality of collagen, a certain amount of inflammation is needed under certain basic conditions such as the required levels of mediators, hormones, and cell migration. The aging

process involves more than just collagen and elastin restoration. We must understand that there are different needs in terms of stimulation. Therefore, patient assessment becomes a key point in understanding whether just one treatment such as MFU-V is enough to induce collagen formation, or if other procedures that up-regulate mediators and cell migration[23] are also needed during the first phases of healing started by MFU. These include calcium hydroxylapatite (CaHa) or poly-L-lactic acid (PLLA), as shown in a recent study where the histology of the skin after combining both procedures on the same day resulted in larger collagen and elastin formation by increasing stimulation during the first phases of the healing cascade.[24]

The Devices

Most HIFU devices have more than one transducer depth and size focus (Table 1). Macrofocused transducers are used for fat reduction, and are not safe for collagen stimulation because the TCPs are too large and the pulse duration is usually longer. Microfocused transducers have different frequencies. A MFU-V transducer with a frequency of 4 MHz has a depth of 4.5mm and creates a TCP of 1mm^4, while a transducer with a frequency of 7 MHz has a 3mm depth and creates a TCP of 0.3mm^4, and a transducer with a frequency of 10 MHz has a 1.5mm depth and creates a TCP of 0.18mm^4 (Figure 1).[6] All devices work with one handpiece, and the transducers are interchangeable and should be used over a thin layer of gel to guarantee good contact with the skin (See video http://jddonline.com).[10]

How to Achieve the Best Results

Patient assessment is far more complex than just observing the complaints of the patients who arrive at our office. Sometimes it is hard to estimate the number of lines or which procedures should be combined to provide a natural and satisfactory result. For didactic reasons and to try to facilitate a certain procedure on why and when to use a certain number of MFU-V treatment lines and depths, as well as when to combine other treatments, the authors have divided patient assessment into five steps:

1) Assess – expectations, features
2) Decide – which depth to customize
3) Select – choose a number of lines to achieve the objective
4) Plan – combination, if needed
5) Treat – documentation, safety, and comfort

1. Assess

In this step, there are two main goals:

A. Expectations

Identify patient expectations based on the MFU procedure alone. A retrospective study[24] showed discordance between physician and patient regarding satisfaction with results. Sometimes, even though the physician graded the result as only mild improvement, the patients were happy and satisfied, but the opposite can also occur. Sobanko et al[26] showed how important psychological aspects are in improving appearance and how patient motivations for the treatment can differ. Also, patient

FIGURE 1. Schematic illustration of different frequencies present in each different transducer and the wave size and TCP sizes.

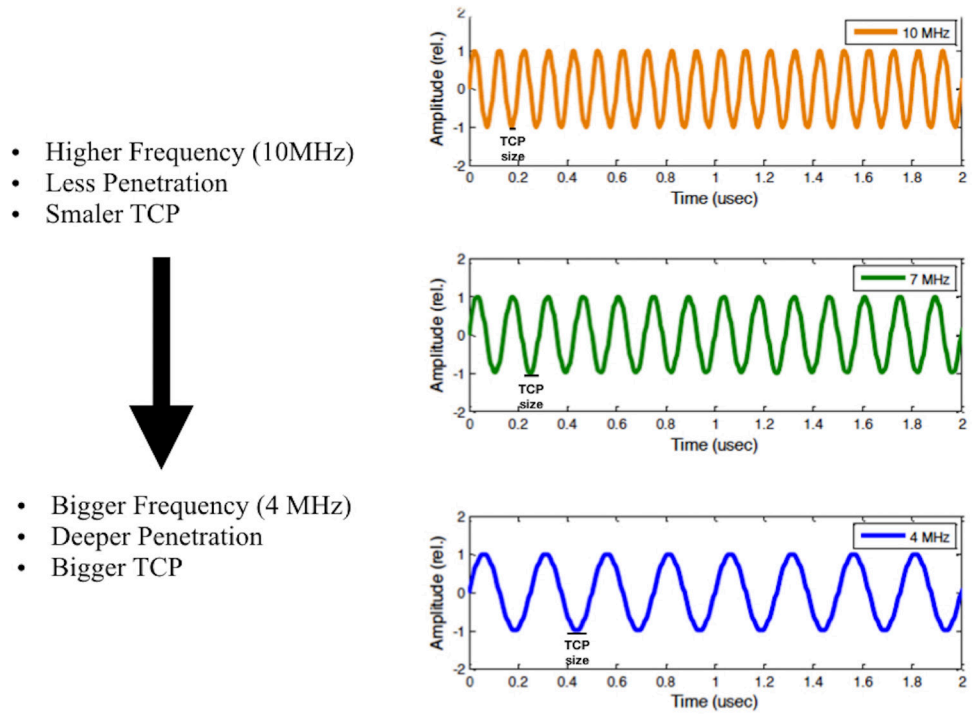
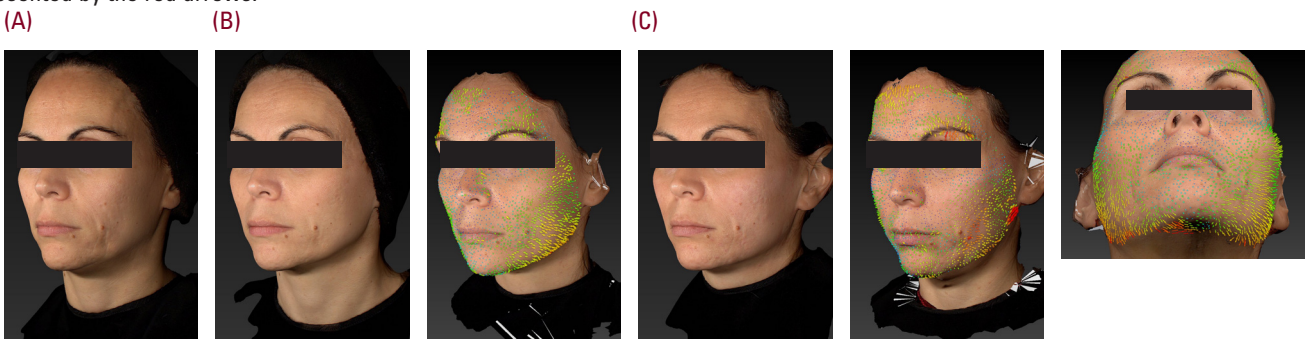


FIGURE 2. A patient after MFU-V treatment. (A) 3 months after treatment showing that the displacement occurred in the direction of the tragus area in the face and in the direction of the mandible border in the superior neck, (B) 3 months after injection of dilute CaHa in face showing a more intense displacement in same direction (horizontal) and in vertical manner in superior neck, and (C) 1 month after injection of CaHa as a filler to the zygomatic arch, lower mandible border, and angle of the mandible showing a new displacement more perpendicular to the skin layer represented by the red arrows.



satisfaction can be enhanced with a close interaction with the physician.[27]

B. Vectors and Severity

Assess the patient's real needs regarding vectors and procedures needed to meet patient expectations. This is the moment where the physician should decide and make clear if, given the level of expectation, the patient is a candidate for a single or combination treatment. In 2005, Marten and Connell[28] described ways of evaluating severity and different patient needs before facelift.

Through different facial positions, the severity of the loss in one specific vector (horizontal, vertical, or projection) needs to be identified to decide if MFU-V alone is the perfect indication as each procedure corrects a different vector (Figures 2 A–C).

One way of assessing involves using the severity scales for face, neck, and chest aging, and other areas such as knees, buttocks, and anterior and posterior thighs.[28-33] According to patient self-assessment scores, the necessary treatment intensity or frequency, the number of treatment lines, or number of repeated treatments, or if the severity indicates that more than one procedure is indicated, can be discussed (Figures 3 A,B).

FIGURE 3. Pre-MFU-V (A) and after 3 months (B). Difference in scale score (right side 2, left side 3) showing improvement related to differences in height of mandible and angle of mandible projection. In these cases, not only horizontal correction of the left side would be needed, but also vertical enhancement of the mandible height and angle.

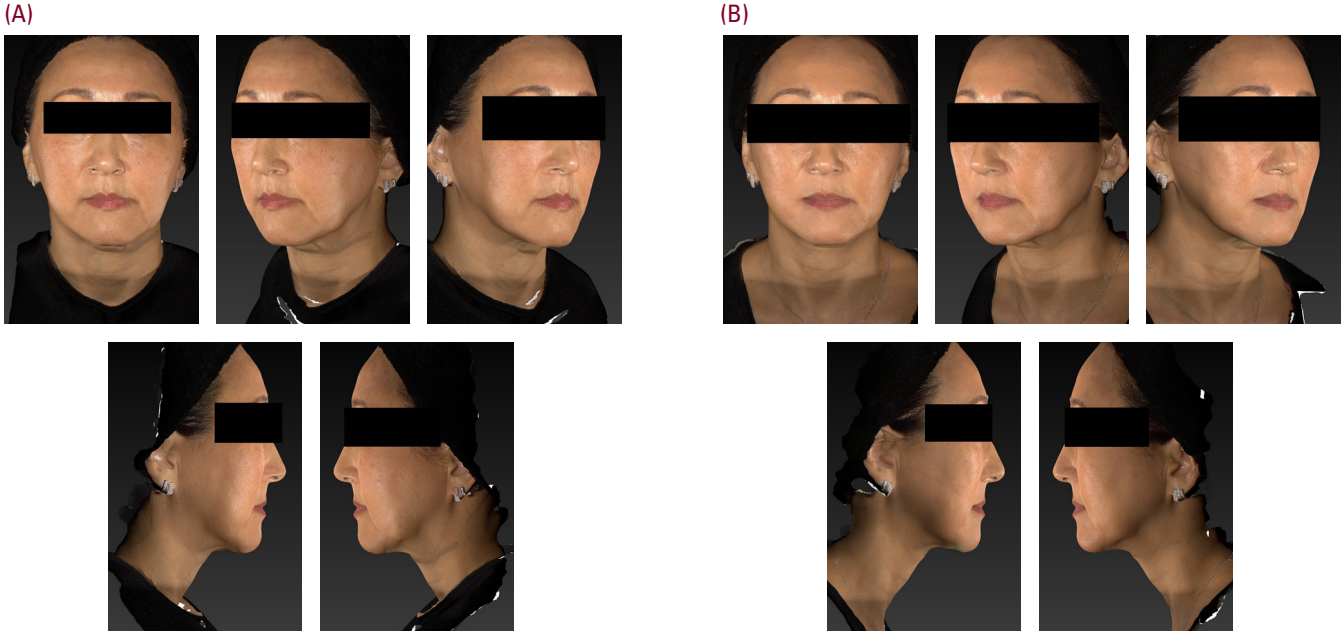


FIGURE 4. Ultrasound image (DeepSee®, Ulthera System) showing difference in depth of the SMAS in face buccal space at 4.5mm (A) and masseteric space 3.8mm (B). Should be treating with 4/4.5mm and 7/3.0 buccals space and change to 7/3.0mm with pressure and 10/1.5mm in masseteric area.

(A)

(B)

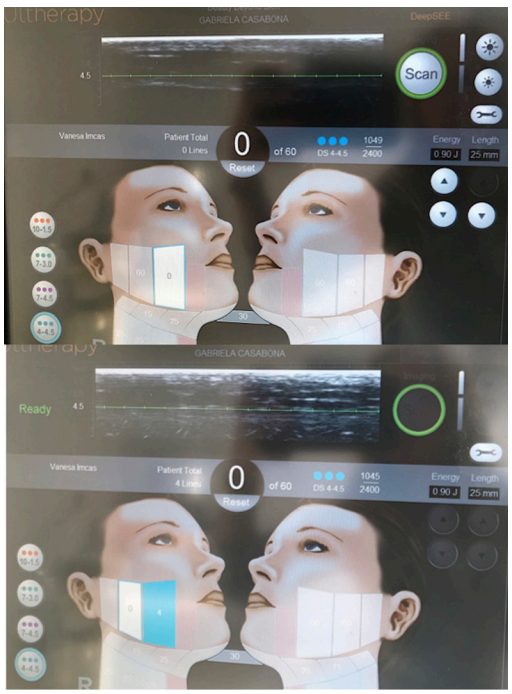


FIGURE 5. Patient before MFU-V (A), after 3 months of non-customized MFU-V treatment (B), 3 months after second treatment, and 3 years later showing a much better improvement (C).

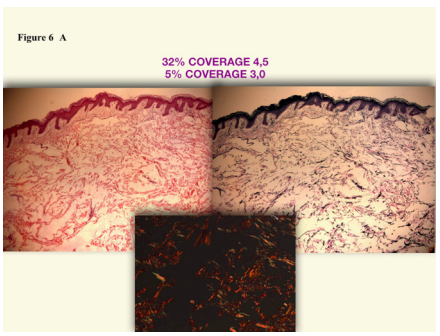
(A) (B) (C)

2. Decide

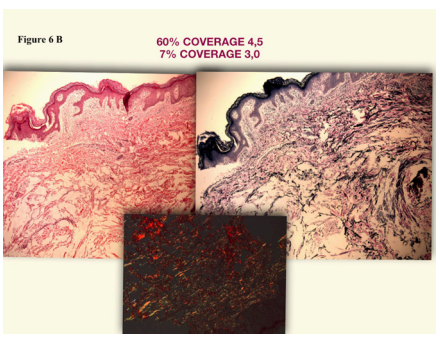
At this point, the MFU-V depth to achieve the desired outcome needs to be decided. There are two possible goals with MFU-V: skin lifting or skin tightening. For a lifting effect, the SMAS or superficial fascia system (SFS) needs to be targeted. The number of TCPs required to create sufficient tightening and to deposit sufficient new collagen and elastin to achieve a lifting effect needs to be determined. Skin tightening can be achieved by making the skin thicker and, therefore, denser and firmer.

FIGURE 6. Skin stained with picrossirius after treatment with MFU-V coverage 32% with 4.5mm and 5% with 3.0mm (A), and coverage 60% with 4.5mm and 7% with 3.0mm (B). The stain is used to color collagen fibers and shows more concentration in (B) where the number of lines and coverage was higher.

(A)



(B)



To decide the depth of the SMAS and SFS, the physician must master the ability to identify these layers through real-time ultrasound visualization. This is important because a recent study by Casabona et al[34] showed that the SMAS and SFS can change with age, gender, and body mass index (BMI), and in different areas of the face and body (Figures 4 A,B).[35,37] Another study[38] showed that patients who received a customized transducer selection based on ultrasound visualization were far more satisfied with results after MFU-V alone (Figures 5 A–C). In conclusion, if the MFU-V treatment lines are not directed exactly to the appropriate tissue layers, the procedure can be less effective, leading to frustration with the final results.

3. Select

In this step, the physician should check the number of lines needed based on two parameters: the transducer to use and the coverage area provided by each one, according to appearance, severity, and treatment goal. The amount of collagen that MFU-V can produce depends on the number of lines and therefore the linear coverage or density of lines in the same area (Figures 6 A,B). A recent study published by Sasaki et al[39] showed more treatment lines produce better clinical results. It would be logical to conclude that different severities would require different density of lines or even different number of

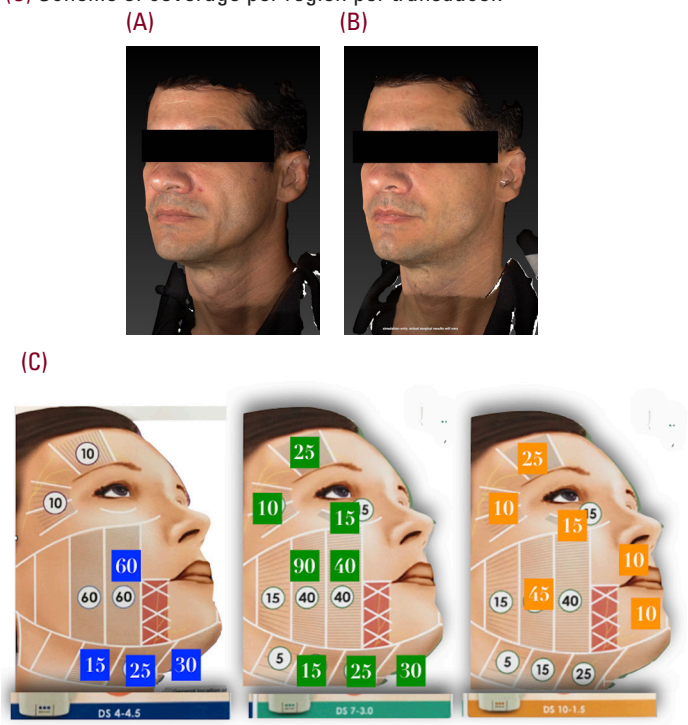
layers treated to achieve the same endpoint in same vector (horizontal or vertical depending on area). As mentioned before, the recommended protocol of transducers per area needs to be adapted according to SMAS or SFS depth. Therefore, the coverage needed to be adapted to bring the same result once the TCP area of the 4mm/4.5 MHz transducer (1mm^3) is much bigger than the 7mm/3.0 MHz (0.3mm^3) or 10mm/1.5mm MHz (0.2mm^3) transducers. The author developed a table using the ruler provided with some HIFU devices that has an area of 2.5cm x 5cm and is used to mark and distribute the determined number of lines when delivered by a transducer in a certain area of face and body (Table 2). This table might help to convert the number of lines from one transducer to the other if needed. Although, it is important to point out that we do not have data on what is the ideal conversion of one transducer to the other to keep the same clinical result. The authors recommend these corrections when changing transducers: 4/4.5 to 7/3.0–50% more lines of standard protocol, 7/3.0 to 10/1.5–30% more lines of the standard protocol (Figures 7A–C).[40]

4. Plan

In this step, the most important assessments are the vectors involved in the aging appearance for each patient and each area of complaint. The face, neck, and chest have different ways of aging, and the same layers of skin are disposed differently in these three areas. Also, it is very important to evaluate the patient in dynamic and resting conditions because this will provide a hint about which layer is more important to treat to effectively address the specific patient complaint.

- Face: Only MFU-V can provide correction in a horizontal manner on the face, tightening the skin and SMAS from the corner of the mouth to pre-auricular area (fixed part of the SMAS).[39,41]
- Neck: Only MFU-V can provide correction in a vertical manner in the neck, recreating the mandible definition by tightening the platysma and skin from its origin (mandible region) and insertion (clavicle).[39]
- Décolleté: Only MFU-V can provide correction in a vertical manner on the chest as shown in clinical experience.[42,43]

FIGURE 7. Pre-treatment with MFU-V (A) and (B) after 3 months showing conversion of coverage from one transducer to the other. (C) Scheme of coverage per region per transducer.



Other procedures such as biostimulators and fillers can enhance the strength of other vectors such as horizontal or projection on the frame of the face, neck, and chest (Figure 8).[44,45] They can be boosters (enhance collagen stimulation same areas) or highlighters (enhancing visual result of MFU-V by restoring the structure of bone and fat creating a stretching effect on the tissue envelope from SFS to epidermis). The more vectors you treat without overtreating one or the other, the more natural results look.

TABLE 2.

Ruler Area and Transducer Coverage Based on Number of Lines

Ruler				Coverage			
Lines	Height (mm)	Length (mm)	Total (mm2)	4/4.5	7/4.5	7/3.0	10/1.5
240.0	50.0	25.0	1250,00	256.22%	163.98%	31.20%	21.67%
120.0	50.0	25.0	1250,00	128.11%	81.99%	15.60%	10.83%
60.0	50.0	25.0	1250,00	64.06%	41.00%	7.80%	5.42%
30.0	50.0	25.0	1250,00	32.03%	20.50%	3.90%	2.71%
40.0	50.0	25.0	1250,00	42.70%	27.33%	5.20%	3.61%
25.0	50.0	25.0	1250,00	26.69%	17.08%	3.25%	2.26%
15.0	50.0	25.0	1250,00	16.01%	10.25%	1.95%	1.35%

FIGURE 8. Scheme of each procedure and each vector per area.

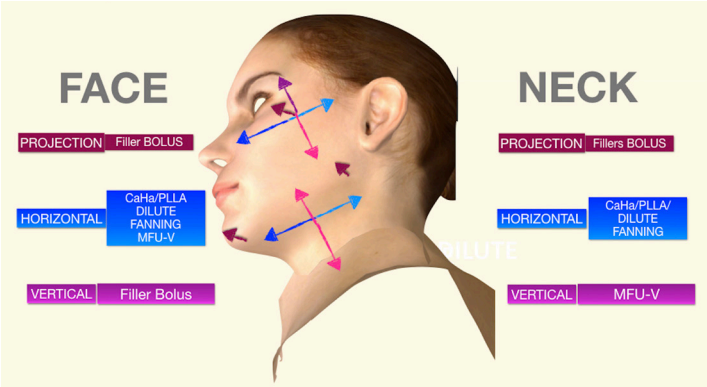


TABLE 3.

Pain Control Measures Prior to MFU-V Treatment[39,42,49]	
Oral	Diazepam (2.5–10mg), ibuprofen (400–1,200mg), or acetaminophen (400–1,000mg) administered 30–60 minutes before treatment Hydrocodone/acetaminophen, 7.5/500mg or 7.5mg/750mg; hydrocodone 7.5mg or 10mg plus diazepam 5mg or lorazepam 2mg
Intramuscular	Intramuscular ketorolac tromethamine 60 mg was given 60 minutes prior to treatment

Also, it is very important in this step to plan if the procedure(s) will be done the same day. Carruthers et al published a consensus on the combination of MFU-V and other procedures with experts recommendations regarding best timing.[46] According to this consensus, it is best to treat in single procedures separated by 15 days to allow recovery from possible adverse effects; however, patients may prefer to have several treatments on the same day. Devices such as MFU-V should be used first, followed by injectables such as fillers, biostimulators, and toxins, followed by superficial treatments such as peels, microneedling, and creams.[46,47,48] One recent publication by Yutskoskaya (2019) showed that combining MFU-V and CaHa on the same day is superior to other timings for combination treatment.[49]

5. Treat

In this step, it is important to ensure patient comfort, that the treatment goes as planned, and that the patient is satisfied. Photography is important to demonstrate that MFU-V was effective with realistic results.[50] It also serves as a quality control tool. Currently available 3D cameras that standardize light exposure and facial position can be used for the face, neck, and chest.

Pain control is an important part of the experience. In some publications, patients evaluated the procedure poorly despite good aesthetic improvements because of the treatment-related pain.[24,42,51] There are different protocols described for pain control, and very few publications on what is most commonly used (Table 3).[39,42,51] Although not mentioned in most publications, in the authors' opinion, after using the device for 7 years, the most efficient and easy methods of pain control are a topical paste containing lidocaine and tetracaine 7%/7% (Pliaglis®, Galderma Laboratories) applied 40 minutes prior to the procedure, oral ketorolac 10mg applied 10 minutes prior to the procedure, and good conversation and energy adjustment during the procedure.

An important safety factor during treatment with MFU-V is to be sure the gel coat being used is not too thick, thus interfering with ultrasound penetration that could possibly cause a burn injury.[52] The distribution of the lines needs to be correct. A certain amount of overlap is acceptable, but stacking treatment lines is not acceptable because it could also cause burns.[52] Before every pulse, be sure the transducer is targeting the right layer to guarantee not only efficacy but also safety, and to avoid adverse events such as nerve damage.[52,53]

Finally, it is important to contact the patient for further evalution in 3, 6, and 12 months. Published data show that due to lack of estrogen, especially in some older patients, treatment response can be slow, and it is important to be in close contact with the patient to manage expectations and results.[20,24]

CONCLUSION

The aim of this article was to give an updated overview of the history and changes of this procedure as seen through an experienced physician's eye. Through this review, it has become clear that in last 7 years since use of the first MFU-V device was approved, the treatment assessment and protocols have changed. However, some retrospective studies make it very clear that patient satisfaction is related not only to the result itself but also to the whole experience of physician-patient interaction, especially regarding expectations, pain, and follow- up.

DISCLOSURE

Gabriela Casabona MD is a consultant for Merz Global. Kai Kaye PhD does not have any conflicts.

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1. What is HIFU ?
   a. It is an ultrasound
   b. It is a focused ultrasound
   c. It is a focused ultrasound with high intensity
   d. All the above

2. What adaptations are needed in FU technology to be finally used as a non-invasive procedure: adequate pulse duration, controlled energy, and depth?
   a. Higher energies, higher frequencies, and better focus
   b. Less focus, lower energy, and lower frequencies
   c. Variable frequencies, higher energy, and higher focus
   d. Variable frequencies, controlled focus, and variable energies

3. What is the main mechanism of action?
   a. Stimulation of collagen through protein shock
   b. Stimulation of fibrotic tissue
   c. Stimulations of extra cellular matrix
   d. Stimulation of collagen and elastin through 2- healing intention cascade

4. What are the 5 steps concerning assessment and treatment suggested in this article?
   a. Assessment, decision, treatment, picture, and post-procedure care
   b. Assess, decide, select, plan, treat
   c. Assess, decide, select, treat, and follow up
   d. Patient conversation and assessment, visualization, treatment, call back

5. Is HIFU treatment always indicated as a single procedure? Can it be combined with other procedures and when should it be combined and indicated?
   a. Yes, only as a single procedure.
   b. It should be combined with fillers and biostimulators when the patient evaluation shows a need for different vector correction or a boost correction in one vector due to severity and it can be done the same day or 15 days apart.
   c. It should be combined with fillers but not biostimulators when the patient evaluation shows a need for different vector correction and it can be done the same day or 15 days apart.
   d. It should be combined with fillers and biostimulators when the patient evaluation shows a need for different vector correction or a boost correction in one vector due to severity and it cannot be done the same day, only 15 days apart.

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1 2 3 4 5

2. The information presented enhanced my current knowledge base

1 2 3 4 5

3. The information presented addressed my most pressing questions

1 2 3 4 5

4. The activity provided new ideas or information I expect to use

1 2 3 4 5

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1 2 3 4 5

6. The activity avoided commercial bias or influence

1 2 3 4 5

Impact of the Activity

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_____

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