# Intense Focused Ultrasound Tightening in Asian Skin: Clinical and Pathologic Results

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BACKGROUND Laxity and wrinkles of the aging face are common cosmetic concerns. Intense focused ultrasound (IFUS), a novel treatment modality for skin laxity, produces thermal effects at various depths while sparing overlying epidermis.

OBJECTIVE To evaluate the safety and efficacy of IFUS in facial skin tightening.

METHODS AND MATERIALS Twenty-two Korean patients with facial laxity were analyzed after a single IFUS treatment. Patient assessments were recorded, and two blinded, experienced clinicians who assessed improvement of nasolabial folds and jaw tightening evaluated photographs of patients and rated skin laxity. Skin biopsies were taken from 11 patients before and 2 months after treatment.

RESULTS Objectively, nasolabial folds and jaw lines were improved in all patients. Subjectively, 77% of patients reported much improvement of nasolabial folds, and 73% of patients reported much improvement at the jaw line. Histologic evaluation of skin biopsy samples using hematoxylin and eosin and Victoria blue stains showed greater dermal collagen with thickening of the dermis and straightening of elastic fibers in the reticular dermis after treatment.

CONCLUSION IFUS is a safe, effective, noninvasive procedure to tighten the facial skin of Asian patients. Improvement is associated with greater production of dermal collagen and straightening of dermal elastic fibers.

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Nonablative rejuvenation (NAR) lasers have become popular tools in the treatment of facial laxity and wrinkles. NAR devices have been designed to induce thermal injury within the dermis while sparing the overlying epidermis. NAR devices in use include intense pulsed light, radiofrequency (RF), neodymium-doped yttrium aluminum garnet (Nd:YAG), and pulsed dye lasers. Although the incidence of adverse effects is lowest with NAR, cosmetic improvements are subtle and inconsistent, and NAR often requires serial treatments over a 6- to 12-month period.[1–3]

Ultrasound-based imaging systems have been used over several decades for clinical diagnosis. Intense focused ultrasound (IFUS) is an energy modality that propagates through tissues up to depths of several millimeters. During the past decade, IFUS has been used as a clinical noninvasive surgical tool to treat tumors, including those of the liver, prostate, and uterus.[4–6] IFUS creates well-defined thermal injury zones to the superficial musculoaponeurotic system (SMAS). IFUS is similar to fractional laser resurfacing in that thermal lesions are fractionated at multiple spots, but IFUS is different in that the thermal lesions occur only in deep dermal tissue.

Several studies have reported a novel IFUS approach in human cadaveric facial tissue and porcine tissue.[7–9] These reports have showed that IFUS produced focused thermal collagen denaturation in the SMAS, inducing shrinkage and tissue tightening. Alam and colleagues[10] reported clinical results of ultrasound tightening of facial and neck skin. The present study is

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the first to investigate the safety and efficacy of ultrasound tightening in Asian facial skin with histologic results.

## Materials and Methods

### Patients

Twenty-two patients (Fitzpatrick skin type III–VI) with facial laxity were enrolled in this study. Mean patient age was 48.5 (range 38–73); two of the 22 patients were male. All patients gave written informed consent for treatment and photographs. Eleven patients agreed to the biopsy procedure. Exclusion criteria were prior cosmetic facial surgery or placement of tissue fillers, scarring in the treatment region, and allergy to topical anesthetics.

### Intense Focused Ultrasound Device

One IFUS device (Ulthera LLC, Mesa, AZ) was used in this study. The handpiece contained a transducer that was used for imaging the treatment region before delivering a series of ultrasound exposures for treatment. The device contained the following three handpieces (in order of most-superficial focus to deepest focus within tissue): superficial, 7.5 MHz with a focal depth of 3.0 mm; intermediate, 7.5 MHz with a focal depth of 4.5 mm; and 4.4 MHz with a focal depth of 4.5 mm. Lower-frequency handpieces have deeper focal depths. Handpieces delivering energy at 7.5 MHz and a focal depth of 3.0 mm and 4.4 MHz and 4.5 mm were used in this study. Each probe delivers a set of pulses in a linear array, with pulses spaced 1.5 mm apart and an entire linear array of up to 25 mm long. The spacing of pulses within each linear array was set at 1.5 mm, allowing 17 thermal coagulative zones created with each probe discharge. Linear arrays are spaced in parallel at 3-mm intervals. Two available hand pieces with distinct focal depths were used with single passes 1 to 2 mm apart.

### Pretreatment Preparation

Topical anesthetic cream was applied to the entire face and allowed to sit for 60 minutes. The anesthetic cream was washed off with mild soap and water.

### Selection of Ultrasound Handpieces

All patients were treated only once with IFUS. Ultrasound gel was applied to the skin, and the handpiece was pressed perpendicularly, uniformly, and firmly to the skin surface. The forehead and temples and the thin malar area were treated with the 7.5-MHz, 3.0-mm handpiece at the following energy setting: forehead, 0.3 to 0.35 J; malar, 0.35 J; temple, 0.35 J. The cheeks and submentum were treated with 4.4 MHz, 4.5 mm at the 1.0 J energy setting and at 7.5 MHz with the 3.0-mm handpiece at the highest energy setting, 0.45 J. The spacing of pulses was set at 1.5 to 2.0 mm. Before treatment, imaging was used to confirm that the handpiece was placed firmly on the skin surface and that the predicted skin depth was correct. On average, 30 treatment lines were delivered to the forehead, 10 lines to each temple, 70 lines to each cheek, and 90 lines to the submentum. After treatment, the ultrasound gel was wiped off.

Clinicians and patients analyzed the treatment results subjectively at 2 months. The principal investigator and the patients gathered clinical data. The investigator gathered photographic documentation using identical cameras and camera settings (Canon EOS-40D, 10.1 megapixels, high-resolution setting, 2816 × 1880 pixels, Canon Corp., Tokyo, Japan), lighting, and patient positioning before and 2 months after the treatment. Two blinded dermatologists (one female and one male) evaluated paired before-and-after photographs of the 22 patients in a randomized fashion to determine whether there was discernible clinical improvement. The dermatologists were not aware of which photographs were taken before and which after treatment. Specifically, if a blinded reviewer detected a change in a particular patient, the reviewer was asked to identify the post-treatment image. If the post-treatment image was identified correctly, the reviewers' assessment was considered to be "improved;" if the reviewer identified the post-treatment image incorrectly, the reviewers' assessment was considered to be "worse." If the reviewer reported no difference between the two photographs, the assessment was considered to be "no change." The criteria for objective evaluations were improved = 1, no change = 0, worse = −1. Objective scores indicating improvement were calculated as the sum of the two clinician's scores. Patients made subjective clinical assessments of skin tightening by evaluating their own photos. Subjective improvement was assessed much improvement = 2, improvement = 1, no change = 0, worse = −1. Side effects of the focused ultrasound treatment were documented at each treatment session and during the follow-up visit.

### *Histological Analysis*

Skin biopsies were taken from 11 patients before and 2 months after treatment. The 2-mm punch biopsies were sampled from the lateral side of the cheek. All specimens were stained with hematoxylin and eosin (H&E), Victoria blue, and Masson's trichrome stain. The two blinded evaluators assessed the pathologic results by examining the histologic photographs in random order, viewing six sections per patient. The area fractions of collagen and dermal thickness were determined using Image J software (http://rsb.info.nih.gov/ij/) on tissue sections stained with Masson's trichrome.

### *Statistical Analysis*

All experimental data were analyzed using paired Student *t*-tests with SPSS 12.0 statistical software (SPSS, Inc., Chicago, IL). All *p*-values were two-tailed, and $p \leq .05$ was considered statistically significant. Summary data are expressed as means ± standard errors of the mean.

## Results

### *Clinical Results*

All 22 patients completed treatment and received follow-up examinations; no patients did not complete the study due to intolerable treatment or side effects (Figures 1 and 2).

Objectively, all patients demonstrated nasolabial fold and jaw line improvement. Twenty of the 22 patients (91%), showed improvement of two objective score values at the nasolabial fold and jaw line. Two patients (9%) showed nasolabial fold and jaw line improvement of one objective score value. The average objective score of nasolabial fold and jaw line improvement was 1.91. Subjectively, 77% ($n = 17$) of patients reported much improvement of nasolabial folds, and 73% ($n = 16$) reported much improvement of the jaw line. The average subjective scores of nasolabial fold and jaw line improvement were 1.77 and 1.72, respectively.

Patients experienced only minimal pain during the treatment session. No patient reported severe pain requiring additional pain relief with analgesia or sedation. All patients had mild erythema and swelling that persisted for 2 to 3 days. Four patients developed numbness along the mandible after treatment on the cheeks that resolved without sequelae 2 to 3 weeks after IFUS treatment. No other adverse events, including but not limited to nerve and muscle dysfunction, bruising, or bleeding were observed; no

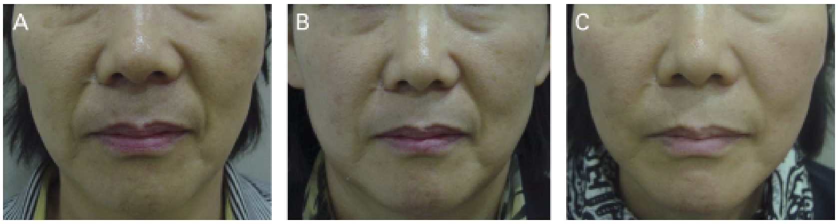


**Figure 1.** Improvement of the nasolabial fold after a single intense focused ultrasound treatment. (A) Before treatment, (B) 1 month after treatment, (C) 2 months after treatment.

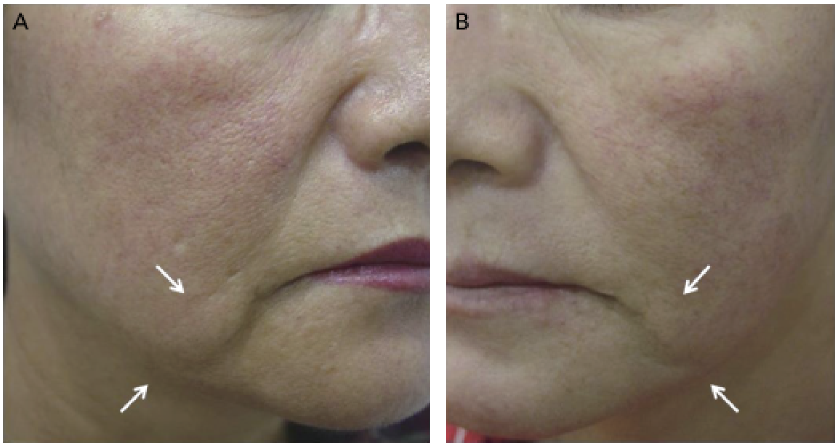


**Figure 2.** Improvement of jaw line and marionette line after single intense focused ultrasound treatment. (A) Before treatment, (B) 2 months after treatment.

serious adverse events occurred. Whitish wheals or striations were apparent on the cheek and submentum of two patients.

### *Histologic Results*

The mean age of patients from whom skin biopsies were taken was 51.6 (range 39 to 73), and all were female. The histology of skin biopsy samples taken before and 2 months after treatment demonstrated significant differences. There were more dermal collagen fibers of the reticular dermis after treatment than before, resulting in greater dermal thickness; the mean thickness before treatment was $1.32 \pm 0.18$ mm, versus $1.63 \pm 0.31$ mm after treatment. The average area fraction of collagen in the reticular dermis increased 23.7%, a change that was statistically significant (Table 1). Neither epidermal changes nor inflammatory reactions, assessed using H&E staining, were noted in any of the cases (Figure 3). In skin biopsy samples taken 2 months after treatment, the elastic fibers of the upper and lower reticular dermis were more parallel and straighter in appearance than samples taken before treatment (Figure 4).

## Discussion

Various noninvasive devices have been developed in an effort to treat aging skin.[11] These modalities have primarily focused on treating the superficial layers of the skin because of limitations in penetration depth. One of the most-effective treatments for aging skin is ablative skin resurfacing with carbon dioxide or erbium lasers, which induces sublethal thermal injury to the skin tissue, causing removal of the epidermis, and contraction and remodeling of the dermis. Although ablative skin resurfacing has been proven effective in treating aging skin, patients treated with this modality sometimes have prolonged erythema, infections, and permanent pigmentary changes. For this reason, nonablative skin resurfacing devices, including intense pulsed light, light-emitting diode, RF, Nd:YAG, and pulsed dye lasers have been designed in an effort to reduce the unwanted adverse effects of ablative skin resurfacing.[12] Although these nonablative skin resurfacing modalities have fewer adverse effects than ablative skin resurfacing, the former modality is less efficacious.

Ultrasound waves induce vibration in the composite molecules of a given tissue, and the friction between the molecules generates heat. Ultrasound energy is a new modality in the field of nonsurgical tissue tightening. Deep energy delivery to the level of the SMAS in a fractionated pattern is thought to be most effective in inducing skin tightening.[13] The wedge-shaped thermal defects created by the ultrasound devices investigated reaches beyond the upper layers of the skin into the deep dermis and subcutis. This

**TABLE 1. Average Fraction of Collagen and Dermal Thickness Before and After IF Intense Focused Ultrasound Treatment**

| | *Mean ± Standard Deviation* | | | |
|---|---|---|---|---|
| | *Before treatment* | *Two months after treatment* | *Change, %* | P-*value* |
| Average area fraction of collagen (%) | | | | |
| Papillary dermis | 54.38 ± 10.89 | 55.58 ± 8.22 | 2.2 | .26 |
| Reticular dermis | 52.70 ± 7.79 | 65.18 ± 7.89 | 23.7 | .001 |
| Dermal thickness (mm) | 1.32 ± 0.18 | 1.63 ± 0.31 | 65.9 | .001 |

IFUS, intense focused ultrasound.

modality reduces risk of inadvertent cutaneous injury to the extent that this delivery can separate secondary scatter and absorption in the epidermis from those in the dermis.

For many decades, high-intensity focused ultrasound (HIFU) has been investigated as a tool to treat solid benign and malignant tumors and is now emerging as a potential noninvasive alternative to conventional therapies. In contrast to traditional HIFU, IFUS deposits short pulses within the millisecond domain (50–200 ms). A frequency in the megahertz domain, which avoids cavitational processes, is used instead of the kilohertz domain frequencies commonly used in HIFU. The nominal energy level deposited at each site in IFUS is also significantly lower (0.5–10 J) than with HIFU (100 J).

The IFUS-mediated thermal ablation tissue response is similar to that from other energy-based devices

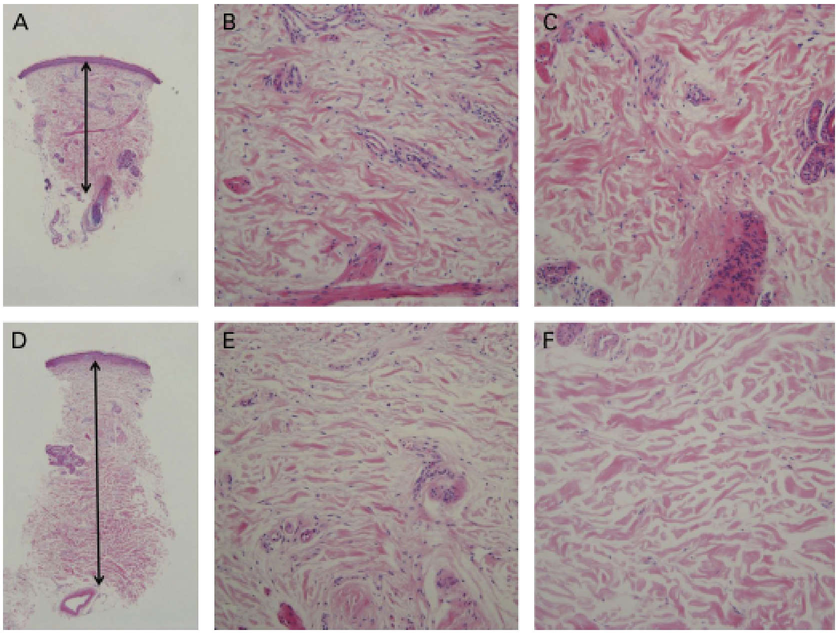


**Figure 3.** Histology of skin biopsy before (A, B, and C) and after (D, E, and F) intense focused ultrasound based on hematoxylin and eosin (H&E) staining. Treatment resulted in fewer dermal collagen fibers, especially in the lower reticular dermis; dermal thickness was also greater. The collagen fibers exhibit a more-parallel and straighter appearance after treatment (arrow length in A: 600 mm, in D: 1,000 mm). (A, B, and C) Tissue samples taken before treatment and stained with H&E. (A) ×40; (B) upper dermis, ×200; (C) lower dermis, ×200. (D, E, and F) Tissue samples taken after treatment and stained with H&E; (D) ×40; (E) upper dermis, ×200; (F) lower dermis, ×200.

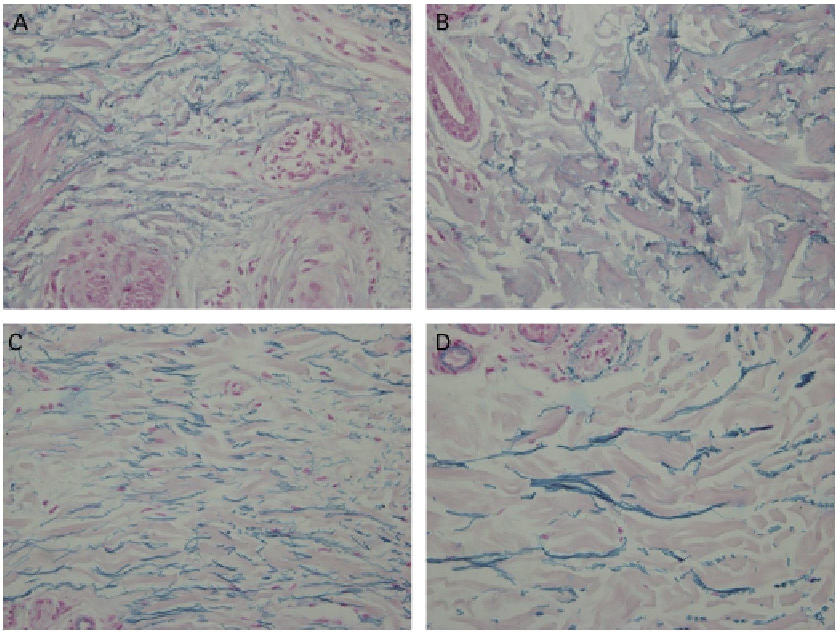


**Figure 4.** Histology of skin biopsy before (A and B) and after (C and D) intense focused ultrasound based on Victoria blue staining. Treatment showing that the elastic fibers are more parallel and straighter in the upper and lower dermis after treatment. (A and B) Tissue samples taken before treatment and stained with Victoria blue. (A) upper dermis, $\times 400$; (B) lower dermis, $\times 400$. (C and D) Tissue samples taken after treatment. C: upper dermis, $\times 400$; (D) lower dermis, $\times 400$.

such as lasers, RF, and combination laser–RF devices.[7,8] Thermal imaging has revealed that the energy of RF delivery is much more diffuse, tends to affect the dermis, and travels along connective tissue septae into the subdermis (Table 2).[14] In contrast to monopolar RF (Thermage Inc., Hayward, CA), IFUS is sharply focused.[7] IFUS is able to focus energy within tissue to produce a 25-mm line of discrete thermal injury zones spaced 0.5 to 5.0 mm apart. Thus, most of the energy is deposited in the form of heat in the focal zone of the beam, leaving the surrounding area unaffected. This characteristic allows the induction of numerous unique thermal damage patterns. Using IFUS, tissue may be altered using various arrays of microscopically small focal damage rather than ablating an entire macroscopic area. IFUS allows a rapid healing response from tissue immediately adjacent to the thermal lesions, which is conceptually similar to laser fractional photothermolysis.[15]

In the present study, 77% and 73% patients reported much improvement of the nasolabial fold and jaw line, respectively, as a result of IFUS-mediated tightening occurring after a single treatment. Patients' subjectively assessed clinical improvement was not significantly different based on age or area treated (e.g., nasolabial folds vs the jaw line). Side effects included transient redness, swelling, temporary numbness, and linear whitish wheals. Linear

**TABLE 2. Comparison of Monopolar Radiofrequency (RF) and Intense Focused Ultrasound (IFUS)**

| | *Monopolar RF* | *IFUS* |
|---|---|---|
| Depth of target spot | To subcutaneous fat tissue | To superficial musculoaponeurotic system |
| Width of target spot | Volumetric effect | Fractional effect |
| Need for cooling | Necessary | Unnecessary |
| Imaging | Not available | Available |

whitish wheals were noted in two patients during the use of the 4.5-mm focal depth probe on the cheek and submentum. Inadequate uncoupling of the heat energy to the skin during the operations of these two patients is thought to have induced the wheals. Most patients reported feeling pain during the procedure, but none needed analgesics. The pain tolerance differed between the patients and was independent of age or fat thickness of face.

H&E staining of the facial biopsies sampled 2 months after treatment revealed a greater number of collagen fibers in the reticular and deep dermis. Victoria blue staining of the tissue indicated that the number of elastic fibers was also gretaer in the deep dermis. The skin samples were 2-mm punch biopsies taken from the lateral malar area that did not penetrate to deep tissue. Therefore, any changes in the SMAS were not observed in our study because of the depth of the biopsy samples, which were not deep enough to include fat or the SMAS layer. This investigation is the first ultrasound-induced tissue change study reporting histological data of Asian human skin. We observed increased dermal collagen and rearrangement of elastic fibers in the reticular and deep dermis. These changes are likely due to the heat delivered to the tissue, which subsequently causes collagen regeneration.

A significant advantage of the dermatologic use of IFUS in Asian patients is that the absorption of ultrasound energy is independent of the melanin content of skin. Instead the microscopic and bulk mechanical properties of the tissue determine the absorption in the skin.[16,17] Therefore, in contrast to light-based devices, the action of IFUS is independent of skin color and chromophores. In addition, IFUS creates a sharp focus of the ultrasound beam several millimeters within the skin. The power density of the converging ultrasound beam is therefore much lower as it passes through the epidermis than at its focal point. Only minimal energy absorption and heating of the tissue occurs in the epidermis, which is insufficient to create significant thermal damage. Thermal heating obviates the need for skin cooling to protect the epidermis of any skin type, as is the case with other devices that induce unexpected thermal alterations within the skin. The data presented here show that the use of IFUS in Asian people appears to be safe and effective.

Another advantage of IFUS is that imaging and targeted energy exposure can be accomplished using the same handpiece. High-resolution diagnostic ultrasound imaging provides excellent intraoperative visualization of the facial tissue layers, facilitating precise treatment. As hypothesized in an earlier cadaveric study,[7] if the "suture-like" points of thermal injury could be delivered at the level of the superficial musculoaponeurotic system, shrinkage and retraction at that level may be achieved with minimal risk to the facial nerve.[10] The deep penetration of IFUS could result in nerve injury, but the present study is the first to investigate the detrimental effect of IFUS exposures on the facial nerve or its branches. The results reported here support the safety of IFUS for treatment of facial tissue, with only four of 22 patients (18%) developing temporary numbness along the mandible, and no sequela were reported. No motor nerve injury was apparent,[18] although marginal mandibular nerve branches are located superficially in the face and should not be aggressively treated.

One limitation of this study is that we did not have a standard photographic device and objective parameters to demonstrate mid- to lower facial tightening, although this study is the first report to combine clinical and histologic data supporting the safety and efficacy of intense ultrasound therapy to the facial tissue of Asian patients. We observed that focused ultrasound induces increased collagen fibers and straightening of elastic fibers in the deep dermis of facial tissue. We conclude that the novel treatment modality IFUS offers a noninvasive treatment option for skin tightening in Asian patients. Because the intense ultrasound system selectively delivers heat energy to thermal injury zones in the SMAS layer, we hypothesize that this system also stimulates dermal collagen and elastic fibers in the zone of intense ultrasound treatment.

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