Clinical Ultrafast Laser Surgery: Recent Advances and Future Directions

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***Abstract*—Ultrafast pulsed lasers can be used to achieve remarkable precision during surgical ablation. Through nonlinear interactions with tissue, ultrafast lasers can provide a largely non-thermal mechanism of ablation and a unique ability to create targeted damage within bulk tissue. These advantages have made ultrafast lasers the ideal surgical tool for various novel applications in ophthalmology. Clinical adoption of ultrafast lasers in other surgical applications remains limited in part due to the lack of a means for fiber delivery of ultrafast laser pulses as a flexible, hand-held surgical endoscope. This review provides an overview of the recent advances in bringing this unique surgical tool into the clinic. We discuss fundamental mechanisms and limitations of ultrafast laser ablation, novel techniques for overcoming these limitations, the current state of clinical applications, and conclude with our recent efforts in developing fiber-coupled probes for flexible ultrafast laser surgery and imaging.**

***Index Terms*—laser ablation, surgery, nonlinear optics, biomedical optical imaging.**

I. Introduction

ALMOST since their inception, lasers have been put to use as versatile biological cutting tools. The invention of the laser in 1960 intrigued biologists and clinicians alike with the prospect of a surgical tool capable of creating targeted damage with diffraction-limited precision [1], [2]. Quickly thereafter, a variety of laser surgery applications were developed, ranging in scale from sub-cellular dissection of organelles [3]–[5] and chromosomes [6] to bulk tissue ablation of eyes [7], skin [8], and teeth [9]. Over the next 40 years, the surgical applications of lasers grew and matured, leading to an abundance of discoveries in cell biology [10] and clinical applications throughout medicine, where acceptance has been particularly strong in ophthalmology [11], dermatology [12], and otolaryngology [13].

The development of clinical laser techniques has centered on continuous wave (cw) and nanosecond or longer pulsed lasers. These conventional laser surgery techniques rely predominantly on linear absorption of laser light because the laser intensities are generally too low to induce appreciable nonlinear interaction at practical average powers. Owing to the linear absorption mechanism, photodamage from these lasers is highly wavelength-dependent and thermal in nature [14]. This wavelength dependence can be exploited to create a tissue-selective effect. However it can also result in non-deterministic cutting effects when cutting heterogeneous tissue and can limit efficacy in transparent or low-absorbing samples. Similarly, though laser heating has been used to great effect clinically for both cauterization of laser incisions and tissue welding [15], the diffusion of heat away from the laser focal volume can lead to collateral damage outside the focal volume and may lead to scarring in biological tissues. While both wavelength-dependence and heating can be mitigated or exploited, the linear absorption of laser light throughout the laser-tissue interaction volume leads to increased damage outside the focal volume along the laser path. This lack of axial confinement ultimately limits their precision inside thicker specimens. With the development of utlrafast-pulsed laser sources in the early 1980s, which deliver pulse durations in the range of 100 fs to 10 ps, biologists and clinicians were given access to new predominantly non-thermal regimes of photodamage, which have increased surgical precision to the diffraction limit and beyond.

Thus far, the clinical potential of ultrafast laser microsurgery has barely begun to be realized, with clinical adoption limited to ophthalmic applications. One of the technological barriers to the adoption of this technology is the lack of a means to flexibly deliver the laser light to clinical sites in or on the patient. The goal of this review is to provide the reader with a perspective on both the current state of clinical ultrafast laser surgery development as well as insights into future directions. To that end, the review begins with a brief introduction to the fundamental mechanisms and limitations of femtosecond laser ablation, which provide the constraints that dictate potential areas of application. Here we discuss the fundamental boundaries to the maximum ablation depth and novel strategies to mitigate these limitations.

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TABLE I
REVIEW OF ULTRAFAST LASER MICROSURGERY MECHANISMS. ADAPTED FROM BEN-YAKAR AND BOURGEOIS [24]

Damage mechanism	Photochemical Damage	Thermoelastic Stress Confinement	Optical Breakdown
Intensity threshold	0.26 x 10^{12} W/cm^2	5.1 x 10^{12} W/cm^2	6.54 x 10^{12} W/cm^2
Electron density at threshold	2.1 x 10^{13} cm^{-3} One free electron in the focal volume	0.24 x 10^{21} cm^{-3} Induced thermal stress overcomes the tensile strength of water	1.0 x 10^{21} cm^{-3} Critical electron density for optical breakdown
Description	Free electrons participate in chemical reactions to form destructive reactive oxygen species and lead to breaking of chemical bonds.	Thermalization of the plasma occurs faster than the acoustic relaxation time. Confinement of thermal stresses leads to formation of nano-scale transient bubbles.	Damage is created by high pressure and high temperature plasma and by the accompanying shock wave and cavitation bubble.
Pulse repetition rate	> 1 MHz A large number of pulses are required. For practical reasons high repetition rate lasers are preferable.	< 1MHz Bubble lifetime is 100-500ns. At higher repetition rates and higher irradiances, heat accumulation and long lasting bubble formation can become significant.	

We continue with a summary of the current state of clinical ultrafast laser surgery development in both soft and hard tissues. Lastly, we conclude with details of our recent efforts toward developing a new clinical application, the treatment of scarred vocal folds, and the creation of a fiber-coupled clinical tool capable of delivering femtosecond laser pulses to medical regions of interest for both microsurgery and microscopic visualization of the microsurgery site.

II. MECHANISMS AND TECHNICAL CONSIDERATIONS IN ULTRAFAST LASER SURGERY

Surgery with focused ultrafast lasers is triggered by the generation of an initial population of free electrons through a combination of multiphoton ionization and band-gap (Zener) tunneling [16], [17]. These ionization pathways are nonlinearly dependent on the local light intensity and thus the region of free electron generation is highly-localized in three dimensions within the focal volume. The free electrons may then act as seed electrons for avalanche ionization, wherein an initial free electron is accelerated by the incident laser field and collides with a bound valence electron, thus ionizing the bound electron through impact ionization. This doubling process can then repeat, causing a cascade, until termination of the laser pulse or total ionization of the valence electron population. The final density of this exponentially growing number of free electrons determines the precise mechanism of damage, which can be dominated by photochemical effects, thermoelastic bubble nucleation, or optical breakdown. While the relative contributions of these ionization pathways can vary with pulse duration, the fundamental characteristics of ultrafast laser ablation have been shown to be fairly consistent for pulse durations up to 5–10 ps [16], [18]. Each of the three mechanisms are summarized in Table I and will be discussed briefly below, while the interested reader can find further details in the work of Vogel *et al*. [17] and Joglekar *et al*. [16].

Photochemical damage can occur at relatively low irradiances. Vogel *et al*. theoretically modeled that photochemical effects may begin at peak laser irradiances as low as 0.26 TW/cm^2 [17], which corresponds to one free electron generated in the focal volume of a 1.3 NA objective lens per pulse[1]. In the photochemical damage pathway, energetic free electrons may either 1) cause damage through disassociation of water molecules, leading to the creation of reactive oxygen species (ROS) that can destroy cellular components [19], or 2) participate directly in the bond breaking of other cellular components [20]. It is also possible that non-ionizing multiphoton absorption may aid photochemical damage in structures such as DNA, where the simultaneous absorption of three near-infrared (NIR) photons may be sufficient to cause direct bond breaking due to the widely observed single-photon absorption peak for 260 nm light [21]. Because creation of appreciable photochemical damage requires a large number of relatively low energy pulses, high-repetition rate ($\sim$100 MHz) ultrafast oscillators are required to create useful damage in a reasonable amount of time.

Thermoelastic damage can occur at peak laser irradiances exceeding approximately 5.1 TW/cm^2. In this regime, thermalization of the free electrons leads to rapid, confined heating inside the focal volume. The subsequent thermoelastic stresses generated therein can lead to the formation of transient nanoscale bubbles [17]. Bubble lifetimes near the nucleation threshold are on the order of tens to hundreds of nanoseconds. Because the thermalization of the electrons occurs over four orders of

[1]Unless otherwise specified, the threshold irradiances provided here assume 100 fs pulses with 800 nm center wavelength focused into water by a 1.3 NA lens, in accordance with the model used in Vogel *et al* [17]. Peak irradiance damage thresholds in the femtosecond regime have been shown to be only weakly dependent on these parameters, however.

magnitude faster than the characteristic thermal diffusion time, temperature effects are well confined and it is believed to be the nucleation and expansion of the nanoscale bubble that is responsible for damage in this regime. For ultrafast laser surgery in this regime, amplified laser systems at lower repetition rates are used, both due to the higher pulse energies required and the need to prevent accumulative pulse effects from increasing the extent of damage.

Lastly, damage due to optical breakdown can occur when laser irradiances above approximately 6.5 TW/cm^2 are delivered and the critical free electron density of $\sim 10^{21}$ cm^{-3} can be met and exceeded. At this point, the plasma at the focal volume becomes highly absorbing and the remaining pulse energy acts primarily to increase the plasma energy density. In this ablation regime, the rapid ionization of the focal volume is accompanied by formation of a cavitation bubble and emission of a shock wave, which may induce mechanical damage to the target that extends beyond the focal volume. While optical breakdown can also be induced using up to nanosecond pulse durations, seed electrons for avalanche ionization generally must be provided by linear heating and thermionic emission. Because ultrafast laser pulses can produce their own seed electrons through multiphoton ionization and tunneling, ablation with ultrafast laser pulses can be conducted in the bulk of transparent and minimally-absorbing materials, such as the transparent tissues of the eye.

For peak irradiances above the photochemical damage threshold, multiple pulses in a pulse train can be used to lower the damage threshold through a repetition-rate dependent incubation effect [22], [23], which can be useful for creating optical breakdown without unwanted nonlinear effects, such as self-focusing effects described below, that can effect pulse propagation. Each of the aforementioned damage mechanisms relies on the same rapid generation of free electrons via the nonlinear optical interaction with matter described earlier. As a result of the nonlinear mechanism, ultrafast laser damage in dielectrics has been generally shown to exhibit only a weak dependence on wavelength in the approximate wavelength range of 500–1500 nm [17], [25].

III. Fundamental Limitations of Ablation Depth Inside Tissue and Methods for Overcoming These Limitations

The high peak intensities of ultrafast laser pulses enable the nonlinear interaction with tissue that permits confined ablation inside bulk tissue. However, these high peak intensities also introduce unwanted nonlinear effects that can limit the maximum penetration depth and precision of ablation.

When using ultrafast laser pulses for microsurgery within bulk tissue, the primary limitation to the maximum ablation depth and precision is ultimately the phenomenon of self-focusing. Self-focusing with ultrafast laser pulses occurs when the intense laser pulses create a spatial variation in the refractive index profile via the nonlinear index of refraction, n_2, and the Kerr effect [26], [27]. The Kerr effect arises from the third order nonlinear susceptibility and is thus present to some degree in all materials. As a result, the index of refraction in a Kerr medium is given by

$$n = n_0 + n_2 I(r,t) \tag{1}$$

where n is the total index of refraction, n_0 is the linear index of refraction, and $I(r,t)$ is the irradiance as a function of beam radius, r, and time, t. Representative values for n_2 are approximately 5.4×10^{-16}cm^2/W for water at 804 nm [28] and 2.0×10^{-15}cm^2/W for porcine cornea at 1030 nm [29]. Thus for irradiances delivered during ultrafast laser ablation, the nonlinear component of the refractive index becomes significant and spatially varying, creating the effect of a positive lens. For a collimated laser beam propagating in a dielectric Kerr medium, the self-focusing effect competes with diffraction, with the two phenomena balancing each other when the peak power of the pulse is approximately [30]

$$P_{cr} = \frac{0.471\lambda^2}{\pi n_0 n_2} \tag{2}$$

where P_{cr} is the critical power for self-focusing and λ is wavelength. Beyond this critical power, self-focusing dominates and the pulse begins to collapse and focus before the geometric focus.

For focused pulses the critical power is approximately the same, where the distance to beam collapse is simply shifted by the lens transformation. Due to the temporal evolution of the pulse, self-focusing laser pulses exhibit a "moving focus" [30], wherein the low intensity front and tail of the pulse will focus toward the geometric focus whilst the high-intensity peak of the pulse will focus earlier. In practical cases, such catastrophic self-focusing is often arrested by a combination of factors, such as plasma defocusing from generated free electrons, self-phase modulation and subsequent dispersion reducing pulse intensity, and reduction of pulse energy due to scattering and absorption in turbid media [31]. Nevertheless, self-focusing effects can lead to material modification both leading up to and behind the geometric focus when intense pulses are focused inside bulk material [32]–[35]. Though generally detrimental, this beam filamentation phenomenon can be exploited in some cases, for example in delivering targeted ionizing radiation in tumor therapy [36].

When focusing inside scattering tissue, increasing laser energy is required to reach the damage threshold at the focus as the focus is moved deeper into the tissue due to attenuation following the Beer-Lambert law. Thus as depth is increased, the peak power of the incoming laser pulses are exponentially increased until $P \gg P_{cr}$ and catastrophic self-focusing shifts the focus significantly shallower than the targeted depth.

Fortunately, several approaches can be taken to mitigate the effects of self-focusing in surgical applications. First, because self-focusing depends only on the peak power of the pulse, focusing with a higher numerical aperture (NA) objective can help avoid self-focusing while still achieving optical breakdown. For Corning 0211 glass, which has a critical power at 800 nm of approximately 1.5 MW, Schaffer *et al*. found self-focusing effects to be negligible when focusing with NAs above 0.9 [37]. The critical power in this study was very similar to the critical power of 1.2 MW found by Miclea *et al*. for porcine cornea at

1030 nm [29]. It should be noted, however, that while higher NA can help to avoid the onset of self-focusing, it can also lead to increased spherical aberrations when focusing deep into tissue without use of immersion fluid to match the index of refraction of the tissue [38]. Spherical aberration enlarges the focal volume, particularly in the axial direction, degrading the confinement of ablation.

Second, for pulse durations below approximately 10 ps, optical breakdown occurs without significant free electron recombination during the pulse and the threshold fluence becomes only weakly dependent on pulse duration [17], [18]. In practice, this weak dependence implies that increasingly shorter pulse durations will serve to increase self-focusing, without a commensurate decrease in ablation threshold. For example, a 100 fs pulse[2] with a sech^2 temporal profile, a critical power of 1.2 MW is achieved with only 140 nJ pulse energy, while a 3 ps pulse can contain 4.2 μJ of energy before reaching the same peak power. Thus pulse durations on the order of hundreds of femtoseconds to few picoseconds may be useful to avoid self-focusing effects while preserving damage confinement.

Third, the pulse-to-pulse incubation effects previously mentioned can provide a reduced damage threshold when multiple pulses are delivered during ablation at repetition rates in the kHz regime and above. Subsequently, a series of pulses can be used to create optical breakdown in bulk tissue while keeping the individual pulse peak power well below the critical power for self-focusing.

In summary, to maximize the practical ablation depth with ultrashort pulsed lasers, it is beneficial to 1) maximize the focusing NA while 2) utilizing pulse durations in the hundreds of femtoseconds or low single picoseconds, and 3) using repetition rates in the hundreds of kilohertz where pulse-to-pulse accumulation effects can be utilized without introducing heating or significantly increasing procedure time.

Recently, two novel methods have been proposed that can potentially increase the photodisruption depths inside turbid tissue. The first method, developed by Ben-Yakar and colleagues, proposes to use the near-field enhancement of plasmonic nanoparticles to reduce thresholds for photodisruption [39]–[41]. In this technique, the laser field is strongly enhanced in the nearfield of the nanoparticles when the incident laser frequency coincides with the plasmon frequency of the metal nanoparticles, causing the particles to act as "nanolenses." We have demonstrated a near-field enhancement of 23- and 35-fold during ablation of a silicon surface functionalized with nanoparticles [40] and photodisruption of cells labelled with nanoparticles, respectively [41]. Due to the near-field enhancement of the metal nanoparticles, tissue ablation can be performed with much lower peak power levels which in return helps avoiding the onset of self-focusing. For successful application of this technique, the metal-nanoparticles need to be delivered *in vivo* to the location of ablation, either topically or systemically, and careful attention must be paid to the targeting specificity and clearance of the nanoparticles.

[2]Note that all pulse durations in this document are measured at the full width at half maximum (FWHM).

The second method involves temporal focusing techniques, which have been used to decrease the peak powers of weakly focused laser pulses as they propagate through tissue, thus avoiding self-focusing effects. In simultaneous spatial and temporal focusing (SSTF), a dispersive element such as a grating is used to spatially separate the spectral components of the ultrafast laser pulse. The resulting pulse is temporally as well as spatially dispersed, resulting in a dramatically reduced peak intensity. Focusing by the objective lens serves to spatially confine the spectrally dispersed beam back to a diffraction-limited spot, thus recombining the spectral pulse components and restoring the ultrafast pulse duration at the focus. The reduced peak power of the pulse during propagation reduces undesirable non-linear effects such as self-focusing and filamentation, thereby improving the maximum ablation depth and axial confinement. Using the SSTF technique, Durst *et al*. have experimentally demonstrated temporal focusing of a 1.64 ps pulse at 275 μm from the focal plane down to 84 fs at the focal plane [42]. The use of SSTF to avoid self-focusing has been experimentally demonstrated in ultrafast laser optical breakdown in water [43] and in micromachining [44], [45]. The clinical relevance of SSTF has only recently begun to be explored, with Block *et al.* demonstrating SSTF for ablation in porcine lenses [46]. In Block *et al.*, the authors observed that use of SSTF eliminated nonlinear effects such as focal shift, self-focusing, and filamentation, and exhibited enhanced ablation confinement.

IV. Applications of Ultrafast Laser Surgery

In comparison with nanosecond-pulsed and cw laser ablation of biological tissues, numerous early studies of ultrafast laser ablation have found improvements in the ablated surface quality and decreased regions of collateral damage [47]–[50]. These qualities, coupled with the ability to create confined damage within bulk tissue, have spurred interest in the use of ultrafast lasers as clinical tools for surgery in a variety of applications and tissue types.

A. Ophthalmology

By far, the most significant clinical development and acceptance of ultrafast laser surgery has occurred in the field of ophthalmology, specifically in the application of "blade-free" femtosecond laser-assisted in situ keratomileusis (fs-LASIK). In conventional LASIK surgery, a microkeratome is used to cut a thin flap of a thickness of several hundred microns or less on the cornea. This flap is then pulled back to expose the underlying stroma, at which point an excimer laser is used to ablate the corneal stroma, reshaping it to correct aberrations and improve visual acuity. In fs-LASIK, the femtosecond laser is used to create the flap instead of a microkeratome, thereby improving uniformity and predictability of flap thickness and reducing the incidence of complications [51], [52]. A comparison of a fs-LASIK flap and a traditional LASIK flap is provided in Fig. 1(a) and (b). First clinically demonstrated in 2003 [51] and marketed by IntraLase Corp. (now owned by Abbott Medical Optics), the fs-LASIK procedure has gained wide-spread acceptance with femtosecond lasers being used in 30% of all LASIK procedures

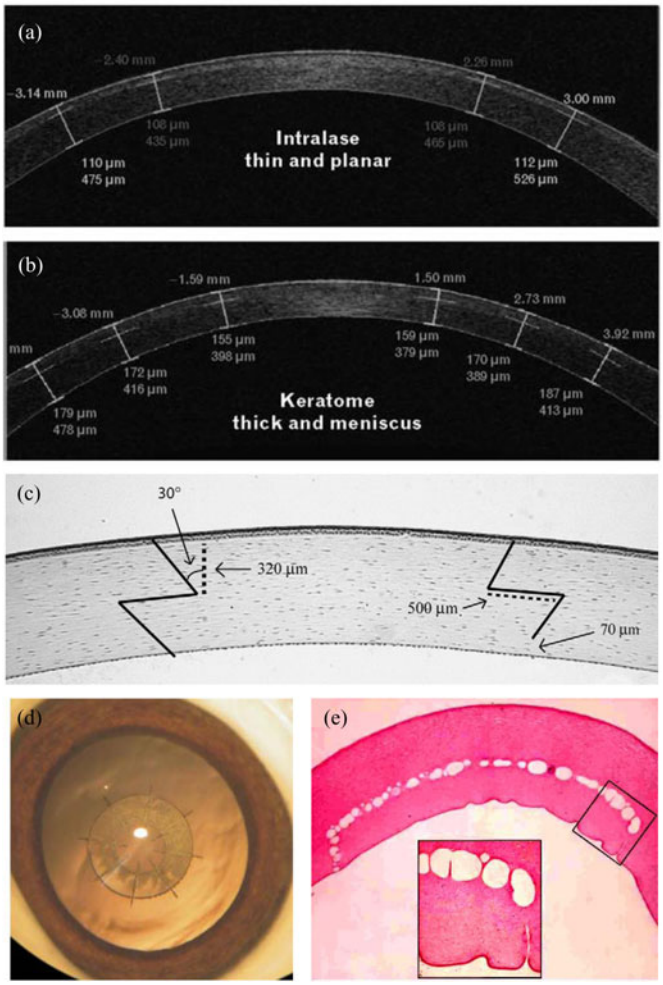

Fig. 1. Representative images of ophthalmic ultrafast laser microsurgery applications. Optical coherence tomography images of LASIK flaps created with, (a) the IntraLase femtosecond laser and, (b) a conventional keratome [52]. The flap is the superficial layer on the cross-section shown. Note that the IntraLase flap is thinner with better uniformity of thickness. (c) Optical image of a donor cornea seated in the eye with a proposed "zig-zag" interface that can be created by ultrafast laser pulses [60]. (d) Light microscopy image of the spoked-wheel pattern cut in the bulk of the lens to produce "gliding planes" in the proposed presbyopia treatment [75]. (e) Histological section of a posterior lamellar graft cut in a porcine cornea [56]. Note that in the applications shown in (c)–(e), the ultrafast laser has enabled complex and/or sub-surface ablations not practical with conventional methods.

by 2006 [53]. Recently, several other commercial ultrafast laser systems have been developed for ophthalmology [54] and fs-LASIK remains the most widely-accepted clinical adaptation of ultrafast laser surgery. This successful translation may be because fs-LASIK 1) targets a region of interest that is easily accessible without the need for fiber optic delivery, 2) capitalizes on the ultrafast laser's strength of making precise cuts within transparent bulk tissue, which uniquely enables the ultrafast laser to replace the microkeratome, 3) provides sufficient improvement in outcome to offset the additional cost, and 4) integrates into a pre-existing laser surgery procedure which avoids major changes in the way the surgical tool interfaces with the patient or with the physician, speeding development and acceptance.

In addition to the success of fs-LASIK, and in large part because of this success, a number of other ophthalmological applications for ultrafast lasers are currently being pursued. Among these, the use of ultrafast lasers for keratoplasty (corneal transplantation) has undergone rapid development and entered clinical practice [55]. In keratoplasty, either a partial thickness (anterior or posterior lamellar keratoplasty) or the entire thickness (penetrating keratoplasty) is removed from the patient's cornea and replaced by tissue from a donor eye. For this procedure, ultrafast lasers have been demonstrated to cut the tissue in both donor and recipient eyes in *ex vivo* animal and human studies since 2003 [56], in *in vivo* animal studies since 2006 [57], and *in vivo* in human patients since 2007 [58]. Compared to a conventional blade, ultrafast lasers offer the advantages of high-reproducibility of cut dimensions and the ability to more easily cut increasingly complex shapes [59], [60] for increased donor-to-recipient tissue surface interaction [Fig. 1(d) and (e).] Recent studies indicate that ultrafast laser-assisted keratoplasty can result in improved wound healing time [61] and reduced astigmatism [58]. Interested readers may find more details about the use of ultrafast lasers in specific types of keratoplasty in the review by Soong and Malta [62] and the references therein.

A number of other ophthalmological applications of ultrafast laser surgery are either being developed or are in the early stages of clinical acceptance. These applications include the use of ultrafast lasers to:

1) replace continuous curvilinear capsulorhexis during cataract surgery [63]–[66],
2) create intracorneal tunnels for the implantation of PMMA ring segments [51], [67]–[70],
3) excise segments of corneal tissue for diagnostic corneal biopsy [71], [72],
4) produce arcuate cuts inside the cornea to correct astigmatism [73],
5) cut planes inside the eye to increase deformability for treatment of presbyopia [Fig. 1(**c**)] [74]–[77], and
6) create pockets for intracorneal implantation of keratoprosthesis [78].

In these applications, with the exceptions of the proposed presbyopia treatment, the ultrafast laser is used to replace mechanical cutting tools, thereby increasing precision and repeatability while reducing the frequency of complications.

B. Soft Tissue Ablation Outside of Ophthalmology

In addition to ophthalmological applications, ultrafast laser microsurgery techniques have been investigated in other soft tissues. In skin, early bench-top studies have indicated that ultrafast lasers can ablate dermal tissue without any observable collateral damage to surrounding tissue [79], [80]. Frederickson *et al*. investigated surface ablation of excised rat dermis and found that thermal damage effects were avoided when using fewer pulses delivered to the focal spot and energies close to the ablation threshold [79]. Conversely, delivery of 35 pulses at 10 Hz repetition rate and pulse energy over ten times the threshold energy led to thermal damage extending 30 μm in this case [79]. The authors propose that this small amount of thermal

damage could be intentionally induced to provide hemostasis for *in vivo* ablation of the dermis, though superficial ablation with thermal collateral damage of this scale is also achievable with less expensive conventional laser sources.

Though dermal tissues are highly scattering compared to the tissues of the eye, several studies have also demonstrated confined sub-surface ultrafast laser ablation in the epithelium and dermis without causing damage to the superficial cellular structure [35], [80], [81]. Specifically, Tse *et al*. succeeding in ablating porcine skin up to 1 mm below the tissue surface as verified by acoustic wavefield measurements [35]. The conditions used in this study resulted in significant self-focusing effects, however, degrading the axial confinement of the laser damage as evidenced by bubble formation detected above and below the focal plane. Further study is warranted to explore the optimum conditions for maximum ablation depth in the absence of self-focusing.

Aside from these initial bench-top investigations, there has been limited development of dermatological applications for ultrafast laser ablation, despite the potential for improved wound healing, reduced scar formation, and improved cosmetic results. Though intended for use with excised tissue, recent studies by Huang and Guo demonstrated the successful use of ablation with femtosecond laser pulses to separate layers of excised dermis for use in skin grafts [82], [83]. This laser surgery method demonstrated improved precision over manual layer separation which reduced tissue waste and allowed many layers to be separated from a single strip of donor dermal tissue.

In addition to dermal tissue, several studies investigated clinical application of ultrafast neurosurgery in the late 1990s [49], [84], culminating in the design of a hollow stereotactic probe for delivery of ultrafast laser pulses into the human brain [85], [86]. The probe utilizes concentric hollow tubes to deliver the laser light and steer the focused beam through a cylindrical focal plane around the probe. Several applications within neurosurgery have been suggested, such as ablation in the third ventricle to relieve hydrocephalus, partial ablation of the thalamus to relieve tremors associated with Parkinson's disease, or the resection of small tumors [49]. More recently, the Schaffer group at Cornell University has demonstrated the use of ultrafast laser ablation to delay and attenuate seizure propagation in mouse models of focal epilepsy [87]. Despite the early interest and development, ultrafast laser ablation of neural tissues is still in infancy. With increasing availability of ultrafast laser systems and further development of ultrafast laser microsurgical tools, new applications may develop as neurosurgeons gain wider access to this technology.

C. Hard Tissue Ablation

In addition to ablation of soft tissues, ultrafast lasers have found numerous applications in ablation of bone and teeth as well. Dental applications of laser ablation have been widely pursued and a number of techniques have achieved a limited degree of clinical acceptance [88]. The driving force behind the development of non-contact laser dental tools has been the desire to avoid the pain and patient discomfort associated with conventional dentistry tools. Laser dental tools can also provide the potential for material-selective ablation by exploiting differences in absorption spectra, thereby limiting the removal of healthy tissue [89], [90]. Initially, development of laser dentistry tools was hampered by the heating of dental pulp leading to tooth necrosis [91]. Even with the use of Er:YAG lasers, which typically emit at 2.94 μm, which have greatly reduced heating for ablation of dentin and enamel [92], the increased procedure time required for laser dentistry has limited acceptance [93]. Conventional dental laser systems are also unable to provide the quality of surface finish required for some procedures, such as the preparation of crown stumps [88]. Lastly, many lasers and conventional diamond burr rotary instruments have been shown to produce micro cracks during material removal, which can weaken the tooth and increase susceptibility to future dental caries [94]–[96].

Encouragingly, early studies of ultrafast laser ablation of both dentine and enamel have found a greatly reduced thermal load while eliminating the formation of micro cracks [50], [97]–[99]. Notably, Rode *et al.* measured the intrapupal temperature of a tooth during 200 s of surface ablation by $\sim$100 fs NIR pulses at 1 kHz repetition rate [98]. The authors found that, while the increase in pupal temperatures could exceed the damage threshold of 5.5 °C [91], the use of air cooling at 5 l/min or higher kept pupal heating at safe levels. By comparison, Neev *et al*. found a negligible temperature increase below 2.5 °C at the back of a 1-mm thick dentin slab during ablation with similar pulses at 10 Hz [50]. These results suggest that in the kilohertz repetition rate regime or above, care must still be taken to ensure safe internal temperature levels are not exceeded. When paired with a cooling, repetition rates in the tens to hundreds of kilohertz are still desirable to achieve satisfactory procedure times. Using a 45 kHz repetition rate, Niemz *et al*. demonstrated ablation rates comparable to Er:YAG lasers and slow-speed mechanical drills [100]. Use of newer fiber laser systems operating at hundreds of kilohertz repetition rate should decrease procedures times even further.

While the use of ultrafast pulsed lasers for dental ablation can reduce the cracking and thermal loading associated with conventional laser systems, the weak wavelength dependence of ultrafast laser ablation threshold means that much of the inherent selectivity between caries (cavities) and healthy dentin is lost. To regain this selectivity, Serbin *et al.* have proposed a means of monitoring the spectra from the plasma created during optical breakdown to identify the material being ablated, which could be tied into a feedback mechanism to control the laser exposure [102].

In addition to teeth, ultrafast lasers have been applied to hard tissue ablation of bone. The use of lasers in lieu of mechanical tools for bone surgery is attractive because of the potential for increased precision and the potential to access surgical sites with less invasiveness. Compared with conventional lasers, the lack of hemostasis that accompanies ultrafast laser ablation may provide fewer complications in bone surgery compared to procedures in more vascularized tissues.

Using conventional lasers, laser ablation of bone is predominantly accompanied by thermal damage, often evidenced by

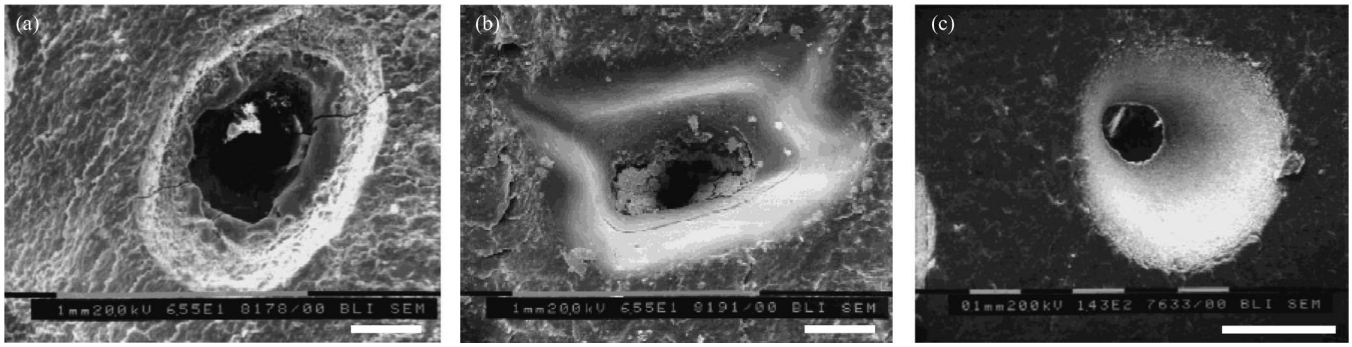

Fig. 2. Scanning electron micrographs of laser ablation in human nail bed. Craters ablated with 100 pulses using (a) Ho:YSGG ($\lambda = 2080$ nm, $\tau = 250$ μs) and (b) XeCl ($\lambda = 308$ nm, $\tau = 15$ ns) using 8–24 J/cm^2 with a 1 mm^2 focal spot (exact fluence per pulse is not reported) (c) Crater ablated with 100 Ti:sapphire ($\lambda = 1053$ nm, $\tau = 350$ fs) laser pulses at 2 J/cm^2 with a 0.2 mm^2 spot size. Note that the thermally affected areas and cracking noticeable in (a) are not found in (b) or (c). Adapted from [101]. Scale bars are 250 μm.

carbonization, and, in the case of pulsed lasers, the generation of significant mechanical stress waves [14]. A delay in the onset of wound healing has been noted in conventional laser ablation of bone and attributed to the thermal damage zone [103]. In addition, acoustic stresses can lead to localized cracking and potentially cause hearing damage in laser surgeries of the middle ear bones [104], an area in which laser ablation has great potential due to the high precision and non-contact nature of laser tools.

Early studies of femtosecond laser ablation in bone and nail tissue showed no observable thermal damage or cracking, as shown in Fig. 2 [50], [101]. Furthermore, in a detailed examination of extracellular and intracellular enzymatic activity on cultured bone tissue after ablation with femtosecond and nanosecond laser pulses, Girard *et al.* observed a dramatic decrease in enzyme denaturation using femtosecond laser pulses [105]. Spectroscopic analysis of the surface of pure hydroxyapatite (a major bone constituent) also showed no change in chemical composition after near-threshold ablation with femtosecond laser pulses [106]. Despite the observed reduction in collateral damage effects, however, a slight delay in wound healing has still been observed in mouse skulls ablated with femtosecond lasers when compared to mechanical tools [107]. In the middle ear, bench-top studies have found femtosecond lasers to improve ablation surface quality for stapedotomy while reducing thermal and mechanical collateral damage compared to conventional lasers [108]–[110].

For practical clinical use, ultrafast lasers must be able to provide material removal at speeds comparable to conventional techniques. Several studies have found the rate of ablation per pulse achieved by femtosecond lasers in hard tissue to be approximately 1 μm/pulse when using near 2 J/cm^2 peak fluence at a 10 Hz repetition rate [50], [101], [108], compared to rates of approximately 2, 7, and 30 μm/pulse found in human nail for Ho:YSGG, XeCl, and Er:YAG lasers, at 4 Hz repetition rate and peak fluences of approximately 24, 12, and 16 J/cm^2, respectively [101].

From this study, the Er:YAG laser (2940 nm wavelength, 250 μs pulse) appears the best choice among the lasers investigated for applications which require high ablation speeds but do not have stringent requirements on cracking and morphology. The femtosecond laser pulses from the Ti:sapphire system (1053 nm wavelength, 350 fs pulse) achieved the highest ablation efficiency, implying that very little energy was wasted as heat or mechanical shock wave. However, in Fig. 2(b), the craters created by the XeCl laser (308 nm wavelength, 15 ns pulse) appeared to match the quality of the femtosecond laser-created craters while providing a seven-fold increase in ablation rate for the parameters investigated. The comparable ablation quality indicates that nanosecond laser pulses in the near-ultraviolet (UV) can suffice for precise superficial ablation of hard tissue. Indeed, the excellent surface quality during superficial ablation is why excimer lasers similar to the XeCl laser remain the tool of choice for reshaping the corneal stroma during LASIK, despite the use of femtosecond lasers to create the Bowman's flap to expose the corneal stroma. However, the ablation efficiency of the nanosecond XeCl pulses was found to be an order of magnitude lower than the femtosecond Ti:sapphire pulses. The excess energy in the nanosecond XeCl laser ablation is converted into shock waves [111], which can be damaging to hearing in otological applications and may make ultrafast lasers a more appropriate tool for ablation in the middle ear.

While the ultrafast laser proved to provide the slowest per pulse ablation rate in the study discussed above, the slightly lower per pulse ablation rate of ultrafast lasers can be overcome with higher repetition rates and correspondingly higher average powers. Liu and Niemz investigated using femtosecond lasers to cut through femoral bone using a pulse repetition rate of 40 kHz [112]. Based on these experiments, the authors estimate that a cut through the femur for knee replacement surgery would take approximately 20 min. While the authors cite this speed as meeting clinical expectations, further decreases in procedure time can be gained through further increasing the pulse repetition rate.

Recently, femtosecond lasers have been investigated as a means to treat kidney stones via laser lithotripsy of urinary calculi [113]. In this study, Qiu *et al*. found that very high energy (640 μJ) femtosecond pulses focused with 0.40 NA could ablate urinary calculi in a bench-top microscope. Compared to nanosecond laser lithotripsy with a Ho:YAG laser, the ultrafast laser produced debris that was one to two orders of magnitude smaller and greatly reduced the mechanical shock waves

generated in the calculi. Recently the authors have presented ablation of calculi using a hollow core multimode fiber [114]. The fiber has an inner core on the order of 1 mm in diameter and can deliver ~200 fs pulses with pulse energies of at least 700 μJ [115]. While the delivery of such high energy pulses can be beneficial for developing flexible endoscopic microsurgery applications, the modal quality, dispersion, and attenuation of this fiber are all highly sensitive to bending, which may prove difficult to manage in clinical practice.

The clinical applications discussed in this section, both proposed and realized, take advantage of an increased precision and/or the ability to create confined effects inside bulk tissue. To capitalize on the benefits of increased precision or to target structures in bulk tissue, the microsurgery must have a means of guidance and frequently require a flexible means of laser delivery.

V. Application of Ultrafast Laser Microsurgery for Scarred Vocal Folds

As previously mentioned, the barriers to clinical acceptance of ultrafast laser surgery are lower in applications that leverage the unique ability of ultrafast lasers to create precise cuts inside bulk tissue due to the lack of competing technologies. Similarly, the barriers to clinical acceptance are also lower in applications for which there is no accepted treatment with conventional methods. For these reasons, we have been developing a technique for treating scarred vocal folds wherein focused ultrafast laser pulses create a sub-epithelial space in scarred tissue, which enables localization of injected biomaterials to restore the desired mechanical properties [116].

Vocal fold scarring is a common side effect of surgical treatment of laryngeal cancer and can also result from disease or prolonged mechanical stress. The presence of scar tissue in the vocal folds increases their stiffness, thus degrading or even eliminating voice function (phonation). Current treatment options are very limited. A variety of injected biomaterials have been suggested for restoring the viscoelasticity of the vocal folds [117]. However optimal localization of the material within the scarred tissue is likely to be extremely difficult and unpredictable with injection alone because the injected material tends to follow the path of least resistance, ending up where it is least needed. To address this challenge, we have proposed a treatment in which an injection space is created through sub-epithelial ablation of a planar region in the vocal fold. In a bench-top study on *ex vivo* porcine vocal folds, we have succeeded in creating precisely targeted sub-epithelial voids using 750 fs pulses with 500-nJ pulse energy from a 500 kHz fiber laser, shown in Fig. 3. The use of a high repetition rate amplified fiber laser also enabled surgical guidance via second harmonic generation (SHG) from collagen using the same laser source, and represents a significant decrease in cost, size, and complexity over the laser oscillator and chirped pulse amplifier combination frequently used for nonlinear imaging and surgery.

More recently, we have successfully demonstrated localization of a polyethylene glycol- (PEG) based biomaterial stained with Rhodamine dye into the ablated sub-epithelial void of 2×1 mm^2 in a scarred hamster cheek pouch, as shown in Fig. 4. In this study, 776 nm, 3 ps pulses of 1 μJ energy were delivered at 300 kHz from a fiber laser to create sub-epithelial voids 90 μm below the tissue surface using a 0.75 NA, 20$\times$ objective (Nikon, PlanApo). When injecting without sub-epithelial voids, we observed a back-flow of the injected biomaterial along the point of injection [Fig. 4(a)], which ultimately prevented localization of the biomaterial at the desired location. Specifically, Fig. 4(a) shows that the fluorescence observed after injection without a void is in fact originating from biomaterial that had flowed back out to cover the tissue surface, and is removed by wiping the tissue after injection. In contrast, the presence of sub-epithelial voids provides a space for the biomaterial, which greatly reduced back-flow at the injection site and resulted in a lasting localization of the injection material [Fig. 4(b)].

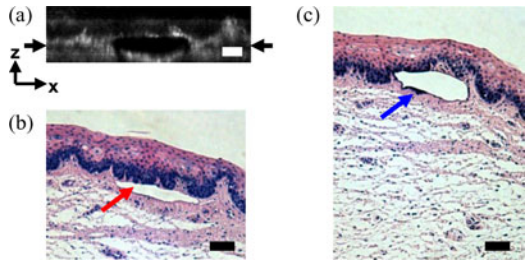

Fig. 3. Histological follow-up of voids created in porcine vocal fold with 500 nJ pulses. (a) Cross-sectional second harmonic generation image of a void ablated approximately 100 μm beneath the tissue surface. Black arrows denote the plane targeted for ablation. (b) Follow-up histology of the void shown in (a). Red arrow indicates sub-epithelial void created by ultrafast laser ablation. (c) Histology section of a different void in the series. Blue arrow indicates small section of epithelial nuclei that were separated out of the epithelium during ultrafast laser ablation. Note the thicker void and the thinner epithelium in comparison with (b). Histology images are stained by H & E. All scale bars are 50 μm. Modified from [116].

VI. Recent Developments Toward Endoscopic Ultrafast Laser Surgery

Many clinical applications require flexible delivery of the surgical laser pulses to the clinical region of interest using fiber optics. While fiber optic delivery is common practice for many conventional cw and long pulse lasers, fiber propagation poses several challenges for ultrafast pulses. The first challenge is that of group velocity dispersion (GVD). GVD occurs when the velocity of light exhibits a dependence on the wavelength of the light, causing the different spectral components in a single laser pulse to travel at different speeds. Shorter laser pulses necessarily contain greater spectral bandwidth so that, when all spectral components are in phase, interference among the spectral components leads to a short pulse in the time domain. The relatively large spectral bandwidth of ultrashort pulses makes them susceptible to GVD, which arises primarily from either material dispersion or waveguide dispersion. First-order linear dispersion can commonly be compensated for through the use of either prism pair or grating pair to introduce GVD of an opposite direction, in what is known as pulse chirping.

Through the optical Kerr effect and n_2, described earlier, the speed of light can also depend on the instantaneous pulse

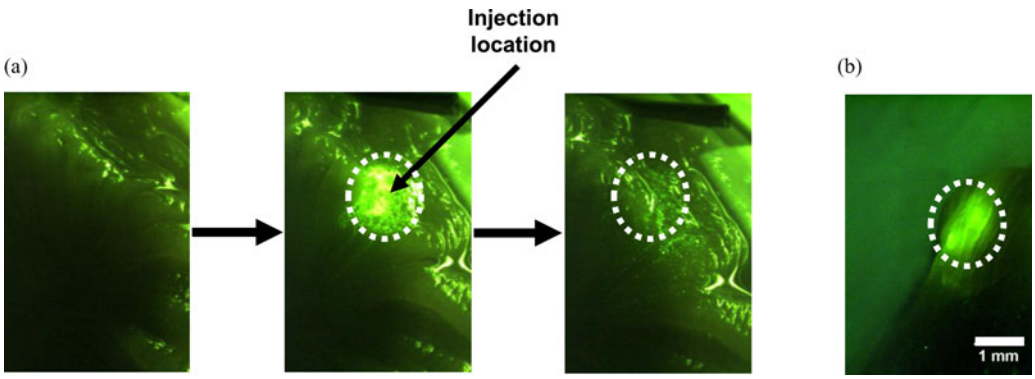

Fig. 4. Injection of PEG30 biomaterial into scarred tissue with and without ablation. Fluorescence images of (a) injection without ablation, from left to right: before injection, just after the injection, and after cleaning the tissue surface showing that it was not possible to inject and localize the biomaterial inside the scar tissue. The dashed lines indicate the region of injection. (b) Injection into an ablated void of 2×1 mm^2 size after wiping of tissue surface. The fluorescence signal originated from the Rhodamine dye embedded in the biomaterial. In this trial, successful localization of the biomaterial was only possible when injecting into an ablated void. Scale bars are 1 mm.

intensity for high peak power laser pulses. In this case, the change in the local speed of light during the propagation of the pulse can create a phase shift across the pulse. This phenomenon is referred to as self-phase modulation (SPM). Because new spectral bandwidth is being created during SPM, the onset of SPM alongside GVD can result in accelerated pulse broadening in media with normal dispersion until the peak power is no longer sufficient for SPM. In this manner, SPM can lead to nonlinear dispersion properties, particularly in conventional optical fibers where GVD is nearly always present and high peak powers arise due to spatial confinement. This nonlinearity of the dispersion makes pre-compensation with a pulse chirping system extremely difficult and thus SPM must be avoided in delivering high peak power ultrashort laser pulses through normally dispersive media for microsurgery.

In the absence of SPM, such as during propagation through air-core photonic bandgap fibers, waveguide dispersion can be compensated for and ultrafast pulses capable of initiating optical breakdown in cells and tissues can be delivered [118]. In this case, the limit to the maximum deliverable peak power becomes the damage threshold of the optical fiber during coupling. This limitation can be addressed by using fibers with a larger air core or by increasing the pulse-chirping prior to the fiber to reduce the peak intensity during coupling while appropriately increasing the fiber length to restore the ultrafast pulse duration at the sample.

In addition to flexible delivery, full realization of the potential surgical precision of ultrafast laser ablation would benefit from image guidance that can resolve the features to be ablated. Nonlinear optical techniques, such as multiphoton excited fluorescence, SHG, and third harmonic generation microscopy (THG), can utilize the ultrafast microsurgical laser at reduced pulse energies to provide imaging signals. By scanning the laser beam, images of the surgical site can be created with sub-cellular details. Nonlinear imaging signals can provide both molecular and morphological information while potentially using the same microsurgical laser. As demonstrated in the vocal fold study described in Hoy *et al*. [116], image guidance offers crucial feedback for localization of the ablation site and for providing visual confirmation of the success and extent of ablation. In this study, the presence of increased collagen just below the epidermis acts as a natural SHG marker of the target area. Similarly, Farrar *et al*. have demonstrated the myelin specificity of THG [119], which could potentially guide ultrafast laser neurosurgery in the spinal cord to avoid damaging axons and make THG an ideal tool for the study of myelin loss and recovery.

Our group has been developing fiber-coupled ultrafast laser surgery probes. The first probe, shown in Fig. 5(a), consisted of a 1-m air-core photonic bandgap fiber for delivery of amplified and unamplified femtosecond laser pulses, a microelectromechanical system (MEMS) scanning mirror, a micro-optical system of aspheric and gradient index (GRIN) lenses for beam delivery and focusing. This probe also incorporated a large-core, large-NA fiber for collection of emitted photons from multiphoton fluorescence and SHG, thus enabling the use of low-energy high-repetition rate laser pulses for surgical guidance by nonlinear microscopy [118]. As mentioned above, the use of the air-core photonic crystal fiber avoids damage to the delivery fiber and nonlinear broadening of the pulse through self-phase modulation while maintaining a single-mode laser beam. By using suitable compensation for waveguide dispersion, the probe delivered 180 fs laser pulses at 780 nm to the focal plane, with resulting peak irradiances in excess of 14 TW/cm^2, well above the threshold for optical breakdown. With this first probe, precise image-guided cellular surgery was demonstrated by imaging fluorescently labeled breast carcinoma cells in cell cultures and scattering phantoms and then ablating selected single cells, shown in Fig. 5(d). While this probe demonstrated the potential for image-guided ultrafast laser surgery in a fiber-coupled probe, the dimensions of this probe would require an 18 mm diameter delivery channel, which precluded endoscopic delivery.

A second probe was developed based on the same architecture which reduced the probe size to less than 10 mm in diameter [120], as seen in Fig. 5(b). Compared to the first probe, the second probe improved the lateral and axial resolution by 20% and 40% to 1.27 and 13.5 μm, respectively, while reducing the diameter by almost half. Design analysis demonstrated the potential for further improvement with the use of custom lenses.

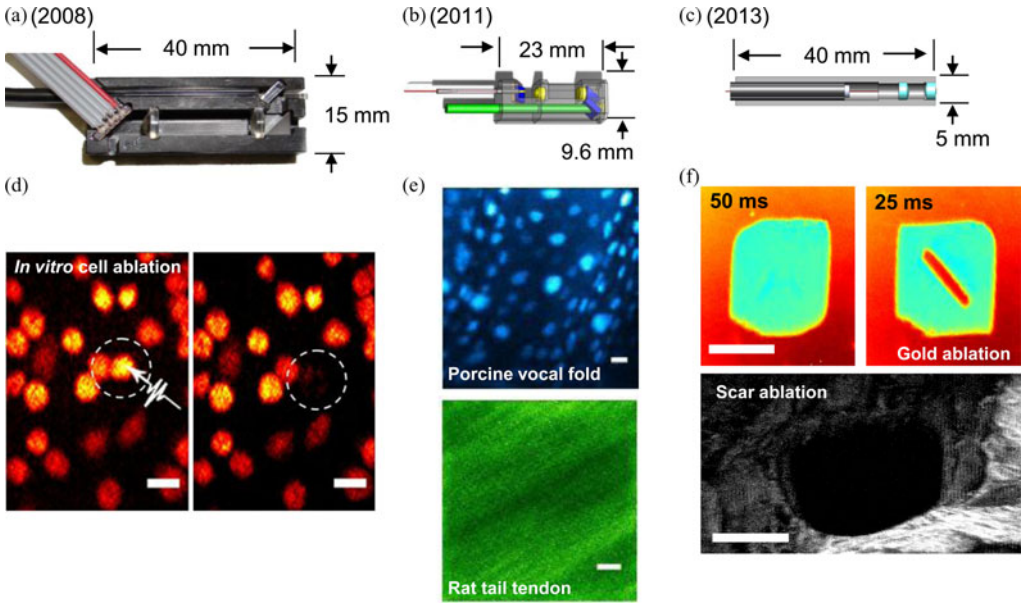

Fig. 5. Three generations of endoscopic ultrafast laser surgery probes. Photograph of the (a) 18-mm probe [118] and schematics of the (b) 9.6-mm probe [120] and the (c) 5-mm probe [121]. (d) Two-photon image of a single layer of live breast carcinoma cells after uptake of calcein AM taken prior to irradiation with high intensity pulses (left) and the same immediately after irradiation with a single pulse at 280 nJ pulse energy (right) using the 18-mm probe. Scale bars are 20 μm. (e) (Top) A maximum intensity projection of a $\sim$70 μm thick two-photon fluorescence image stack of freshly excised porcine vocal fold, stained with Hoechst 3342, showing nuclear details, acquired with the 9.6-mm probe. (Bottom) A SHG image of excised rat tail tendon, showing highly aligned collagen fibers. Scale bars are 10 μm and 5 μm, respectively. (f) Ablation of a 30-nm gold coated glass slide using the 5-mm probe, scanned for 50 ms (left) and 25 ms (right) durations in a Lissajous pattern. The entire gold within the FOV is successfully ablated at durations of 50 ms and above. Ultrafast laser drilling through an *ex vivo* 70-μm thick scarred hamster cheek pouch using 200 nJ pulse energy (bottom); an *xy* maximum intensity projection acquired using a benchtop nonlinear microscope visualizing SHG following ablation. Scale bars are 100 μm.

These improvements enabled imagining of stained tissues and of intrinsic tissue signals from SHG, as shown in Fig. 5(e) in the upper and bottom images, respectively.

Our most recently developed third probe offers a further reduction in diameter and provides an improved microsurgery speed through utilization of a compact, high repetition rate (300 kHz) erbium-doped ultrafast fiber laser (1552 nm/776 nm, 3 W Discovery, Raydiance Inc.) [121]. This probe consists of a piezoelectric tube actuator for fiber scanning and two aspherical lenses that collimate and focus the light, resulting in a simple in-line optical architecture with 5-mm overall housing diameter, as shown in Fig. 5(c). In this probe, we further improved the lateral and axial resolutions, which were measured to be 1.16 μm and 11.35 μm, respectively. A FOV of 150 $\times$ 150 μm could be scanned in a Lissajous pattern using peak voltages as low as 20 V, complying with safety limits within human body. With the given FOV and resolution, near 100% of the resolvable spots are sampled at least once in only 50 milliseconds. Fig. 5(f) (upper) illustrates ablation of gold on glass samples as exposed to two different scanning durations. The entire FOV could be ablated for 50 ms scanning duration, whereas only $\sim$80% of the FOV could be ablated within 25 ms duration, leaving a small non-ablated area in the middle. These results demonstrate a potential speed of microsurgery as fast as 1 mm^2/s for near total ablation.

Using this 5-mm probe, we demonstrated ablation of *ex vivo* scarred hamster cheek pouch using 200 nJ pulses. We could drill through the fixed tissue, which was approximately 70 μm thick, in under 10 s. Fig. 5(f) (lower) illustrates the post-ablation SHG image of the tissue, acquired with a bench-top nonlinear microscope. Despite the narrow bandwidth of the fiber laser used in this study, this probe could still provide fluences that were higher than optical breakdown in the absence of pre-chirping to reduce laser intensities during fiber-coupling. With further development, this probe can serve as a precise and rapid ultrafast laser scalpel in the clinic.

VII. Conclusion

We have attempted to provide the reader with a brief review of the mechanisms that dictate the range of applications of ultrafast lasers in surgery and a summary of the current state of clinical development. Owing to the nonlinear optical breakdown mechanism, ultrafast lasers are capable of ablating biological material with up to sub-cellular precision and can create confined, largely nonthermal cuts inside bulk tissue. While less expensive UV pulsed lasers can be utilized with similar precision for surface ablation, the ability to create precise interior cuts represents a clinical niche for ultrafast lasers. This ability has been exploited to great effect in the field of ophthalmology, where the transparent tissue of the eye and the preexisting use of laser techniques have lowered the barrier to clinical adoption.

In other areas of medicine, however, ultrafast laser surgery remains predominantly confined to the laboratory where the focus has been on investigating and developing new clinical applications. New clinical applications will likely need to identify areas where the need for precise ablation in bulk tissue justifies a potential increase in cost and complexity over existing techniques or where no other acceptable technique exists. The potential for combined surgical guidance using the same laser system for nonlinear optical imaging may also drive new applications,

such as in neurosurgery with myelin-specific THG imaging. We have highlighted one such application, the creation of subepithelial voids for treatment of scarred vocal folds, which fits both of these criteria. Using ultrafast lasers for both surgery and image guidance, we have shown here that the ultrafast lasers can be used to greatly enhance the localization and retention of injected biomaterials used for treating vocal fold scars.

As new clinical applications are developed, ultrafast laser technology will need to develop alongside them. The size, cost, robustness, and speed of ultrafast laser systems have all improved significantly since their invention, particularly in the case of fiber lasers. Current ultrafast laser systems typically provide repetition rates in the many hundreds of kilohertz to single megahertz range, enabling faster surgical cutting and reasonable imaging times. Meanwhile, such systems deliver pulse durations frequently in the many hundreds of femtoseconds to few picoseconds, which is a desirable range for limiting the effects of self-focusing and thus ablating deeper in tissue. In addition to the lasers themselves, many applications require small and flexible delivery of the ultrafast laser light. Such delivery is possible without sacrificing the quality of the nonlinear ablation or the potential of inline image guidance through the use of photonic crystal fibers and miniaturized optical probes.

As these applications and technologies develop in the coming years, ultrafast lasers have the potential to provide many new clinical solutions and enable creative medical treatments as yet unimagined.

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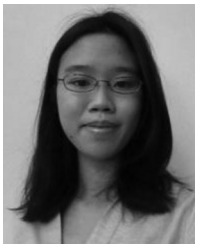

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