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Review

Laser Ablation for Cancer: Past, Present and Future

Emiliano Schena [1,*], Paola Saccomandi [2] and Yuman Fong [3]

[1] Unit of Measurements and Biomedical Instrumentation, Center for Integrated Research, Università Campus Bio-Medico di Roma, Via Álvaro del Portillo, 21, Rome 00128, Italy
[2] IHU (Institute of Image-Guided Surgery), S/c Ircad, Strasbourg 67091, France; paola.saccomandi@ihu-strasbourg.eu
[3] Department of Surgery, City of Hope, Duarte-Main Campus, 1500 East Duarte Road, Duarte, CA 91010, USA; yfong@coh.org
* Correspondence: e.schena@unicampus.it; Tel.: +39-06-2254-19650

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Abstract: Laser ablation (LA) is gaining acceptance for the treatment of tumors as an alternative to surgical resection. This paper reviews the use of lasers for ablative and surgical applications. Also reviewed are solutions aimed at improving LA outcomes: hyperthermal treatment planning tools and thermometric techniques during LA, used to guide the surgeon in the choice and adjustment of the optimal laser settings, and the potential use of nanoparticles to allow biologic selectivity of ablative treatments. Promising technical solutions and a better knowledge of laser-tissue interaction should allow LA to be used in a safe and effective manner as a cancer treatment.

Keywords: laser ablation; cancer therapy; local cancer therapy; thermal ablation; thermography

1. Introduction

Many ablative techniques are being proposed as alternatives to traditional resectional surgery. These include laser ablation (LA), radio-frequency ablation, microwave ablation, high intensity focused ultrasound treatments, and cryosurgery. All these techniques hold the promise of cancer killing while sparing normal tissue. Ablative therapy can also be delivered in a minimally invasive manner, allowing less pain and shorter recovery time. Among the mentioned techniques, LA shows the attractive possibility of being guided through a flexible and small fiber to targets in deep-lying organs.

The first application of laser in surgery dates shortly after its invention, when in 1961 Salon and coauthors investigated its potential as a clinical tool [1]. In the 1980s, the first preclinical and clinical testing of lasers as ablative tools for brain cancer, gastrointestinal tumors (liver and pancreas), and prostate cancer occurred [2,3]. Many different lasers have been proposed for use in surgery. This article reviews the state of the art of the lasers most used in ablative procedures for cancer removal: with particular attention on the characteristics of various lasers, on the factors which influence the treatment outcome, and on the emerging solutions proposed to improve the outcomes of LA.

2. Basic Components of a Laser and Factors of Influence on the Laser Effect on Tissue

LA is performed by using a laser and a medium which transports the laser light inside the tissue. The laser, which consists of a power source, a lasing medium, and reflecting mirrors, provides a monochromatic light (the light is emitted at a specific wavelength), whose wavelength defines the properties of the laser and the interaction with biological tissue. The medium is usually a small diameter (0.2–0.8 mm) flexible optical fiber that transports the laser light inside deep organs. Laser-tissue interaction can be described by three phenomena: scattering, reflection, and absorption. The light absorbed by tissue is converted into heat. Prolonged exposure of tumor cells at temperatures ranging

from 45 °C to 55 °C or short exposure at temperature higher than 60 °C causes irreversible cell damage [4]. Complex mathematical descriptions, based on Arrhenius rate analysis, allow for estimating the cell death as a function of both temperature and exposure time [5].

Heat generation in the tissue, hence the effect of LA, is influenced by a number of factors: laser light wavelength, laser settings (laser power, laser energy, and treatment time), physical properties of the tissue, and the emission characteristics of the optical applicator [6], see Figure 1.

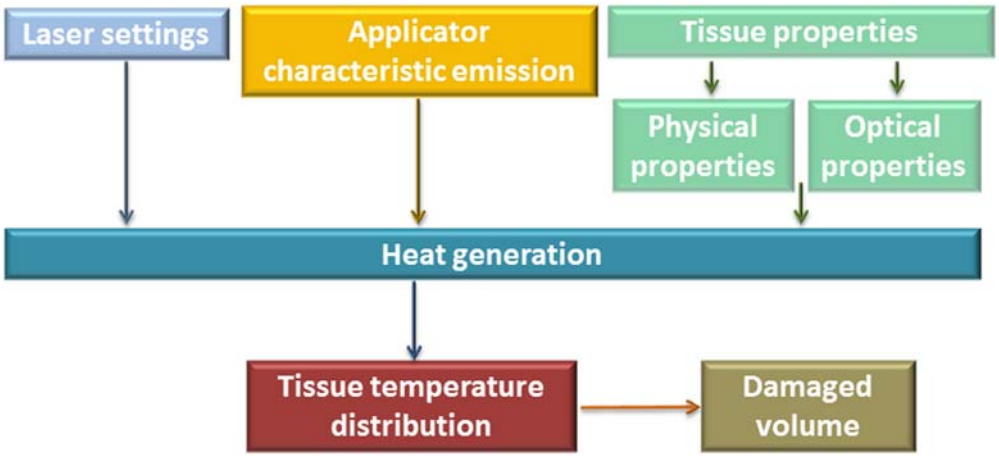


Figure 1. Schematic representation of the factors of laser ablation influencing the volume of tissue destruction.

In order to destroy the tumor without damaging healthy surrounding tissue or minimizing this unwanted effect, all the mentioned factors must be taken into account during the treatment. In particular, a very important parameter used to describe how the laser light is absorbed by the tissue is the absorption length, defined as the tissue depth needed to absorb 63% of the incident light. The absorption length is specific for different laser types (laser light wavelength). It is also related to the optical characteristics of the specific tumor and the surrounding healthy tissue [7]. Lasers with wavelengths strongly absorbed by tissue are employed for superficial treatment. Conversely, in order to treat deep tumors, a high optical penetration depth is required.

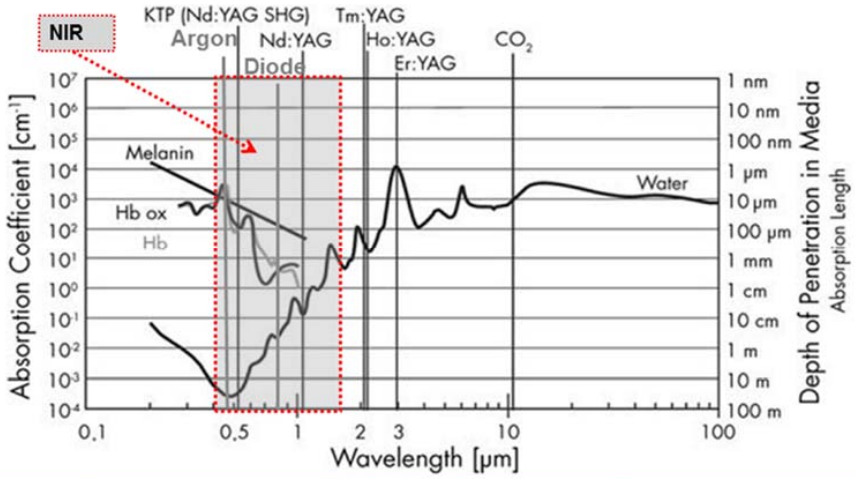
The choice of laser settings is related to the specific effects desired during the procedure. LA can be performed in continuous mode or in pulsed mode. In continuous mode, low laser power (ranging from 2 W or 3 W up to 30 W), and long treatment time (from a few minutes to more than 20 min) are usually employed [8]. In pulsed mode, in which the laser energy is released intermittently in a series of pulses rather than continuously, higher laser power (>100 W) is used. It must be noted that the tissue temperature increase (hence the amount of damaged volume) is not a linear function with respect to the laser settings [9]. Thus, tissue temperature and damage volume plateau with increasing treatment time and laser power.

The emission characteristics of the optical applicator play a great role on the geometry of the damaged tissue. Applicators called "bare-fiber" were employed during the first applications of LA. Basically, they are an optical waveguide with an emitting distal end. Appropriate designs and manufacturing of the emitting surface of the applicators allow for reducing the power density and the temperature on their surface, and allow for controlling the tissue geometry damaged [10]. Sapphire-tipped fibers were introduced to avoid carbonization around the fiber tip [11] in order to penetrate more deeply inside the tissue because charred tissue limits light penetration and tissue necrosis [12]. Then other applicators were designed and validated, such as the cylindrical fiber tip [13] and zebra applicators [14]. Moreover, several solutions based on the development of cooled tip applicators or on the use of multiple bare fibers have been proposed to obtain large and controlled damaged volumes [15–18].

Laser use brings about specific safety concerns. LA is performed by lasers emitting light at a power higher than 0.5 W. Medical lasers are therefore Class IV lasers according to the ANSI (American National Standards Institute) standard (ANSI Z136.1 and Z136.3 combination set: "Safe Use of Lasers and Safe Use of Lasers in Health Care Facilities"). The high power of light emitted by Class IV lasers can damage the eye and skin. As a consequence, administrative, engineering, and procedural measures are used to control laser hazards. All the personnel involved in the LA have to be qualified. All should wear protective eyewear for the specific wavelength and optical density used. Moreover, the access to the room during LA should be controlled, and laser hazard signs indicating the class, power, and mode of operation of the laser should be posted.

3. Lasers in Surgery

As described in the previous section, the effects of laser light on tissue depend on the laser operation mode and on its light wavelength. As a consequence, many different lasers have been used to ablate tumors, in order to obtain different effects. They differ mainly according to their wavelength, hence absorption length (Figure 2).



Laser	Wavelength [nm]	Penetration depth [cm]	Mode
Nd:YAG	1064	≈1–10	Pulsed/continuous
diode	800–980	≈1–50	Pulsed/continuous
Ho:YAG	2100	≈0.04	Pulsed
KTP	532	>1000	Quasi continuous
Tm:YAG	2016	≈0.01–1	Continuous

Figure 2. Wavelength, penetration depth, and modality of work of widely employed medical lasers. The absorption spectra of melanin, hemoglobin, and water are also shown.

When deep penetration is required, lasers emitting infrared light are employed. Diode lasers, with wavelengths of 800–980 nm and Nd:YAG (neodymium-doped yttrium aluminium garnet; Nd:Y3Al5O12) lasers with a wavelength of 1064 nm have an absorption length of approximately 10 cm, as shown in Figure 2. The KTP:YAG laser (KTP stands for potassium-titanyl-phosphate) emits at 532 nm, and is highly absorbed by hemoglobin but deeply penetrates in water. This difference is pointed in the plot shown in Figure 2. The absorption of light is limited to three important components of biological tissue because the analysis of specific organs will result in difficulties, the data are incomplete, and the experimental data regarding absorption values show high dispersion [7]. Superficial treatments were performed with a CO_2 laser (10,600 nm), Thulium (2016 nm), and Ho:YAG (2100 nm) with lower penetration depths (from around 10 µm to almost 1 mm).

Nd:YAG, Ho:YAG, and diode lasers were the original lasers deployed in clinical practice. The Nd:YAG laser (1064 nm) is usually used in continuous mode. It has been for decades the most widely used laser because the high penetration of its wavelength is optimal in the treatment of several tumors. The ablation is mostly performed with bare or cylindrical applicators which allows for ablation zones of up to 15 mm and 50 mm diameter, respectively [19]. The use of cooled applicator allows for improving the radial temperature distribution, avoiding carbonization, and using higher laser power.

Table 1 reports a number of applications of Nd:YAG lasers in surgery.

Table 1. Nd:YAG laser for tumor ablation (y = years; m = months; SR = Survival Rate; HCC = Hepatocellular carcinoma; met = metastases; P = laser power; t = treatment time).

Author	Tumor (Number of Patients)	Diameter of Tumor	Applicator	Laser Settings	Follow Up/Complications
Pacella et al., 2001 [20]	HCC (74)	0.8–4 cm	Bare fiber	P = 5 W t = 6–12 min	SR: 99%, 68%, and 15% at 1, 3, and 5 y
Vogl et al., 2002 [21]	Malignant liver tumor (899)	—	Bare or Cooled fiber	P = 4–5 W bare P = 35–45 W cooled fiber t = 3–28 min	0.1% death 13% of overall complications
Vogl et al., 2013 [22]	Malignant liver tumor (401)	<5 cm	Cooled fiber	P mean for each applicator 34 W	SR: 86.5% and 33.4% at 1 and 5 y
Dick et al., 2003 [23]	Primary and secondary liver tumor (35)	—	Cooled fiber	P = 25 W t = 10–30 min	Mean SR: HCC: 14.6 m (for HCC), 15.2 m (for met) Carcinoid (all patients alive from 1 to 47 m post ablation)
Pech et al., 2007 [24]	Colorectal liver met (66)	≤5 cm	Cooled diffuser tip fiber	P = 10 W per cm diffusor length t = 15–37 min	Median of SR 23 m Major complications rate 2.3%
Ritz et al., 2007 [25]	Colorectal liver met (56)	≤5 cm	Cooled diffuser fiber tip	P = 24–30 W t = 20–28 min	After 6 m follow-up, tumor recurrence in 6 patients Morbidity rate 21.4%
Christophi et al., 2004 [26]	Colorectal liver met (80)	<10 cm	Bare fiber	P = 2–4 W	Overall complications 16%
Windahl et al., 2004 [27]	Penile cancer (67)	<3 cm	—	—	Median follow up: 42 m Local recurrence rate 19%
Lont et al., 2005 [28]	Penile cancer (257)	<3 cm	—	—	Median follow up 106 m Local recurrence rate 37.5%
Meijer et al., 2007 [29]	Penile cancer (44)	—	—	P = 25–35 W	Follow up 3 m–16 y Local disease: 48% of the patients
Schlenker et al., 2010 [30]	Penile cancer (54)	—	Cooled bare fiber	P = 30–50 W t = 60–150 s	Local recurrence: 42%, mean time to local recurrence 53 m
Beer et al., 1989 [31]	Bladder cancer (252)	—	Bare fiber	P = 40–50 W t per pulse = 3–4 s	Total complications 15% Only 1 bladder perforation
J. Ruiz-Tovar et al., 2008 [32]	Bladder cancer (1)	—	Bare fiber	P = 35 W t per pulse = 2 s	Bladder perforation
Beisland et al., 1985 [33]	Bladder cancer (100)	—	Bare fiber	P = 45–50 W t per pulse < 4 s	1 bowel perforation, 2 severe bleeding
Kardos et al., 1994 [34]	Bladder cancer (116)	7 mm of average	—	P = 30–40 W t (per pulse) = 2–3 s	No major complications
Cavaliere et al., 1994 [35]	Breast cancer (1585)			P = 20–30 W t (per pulse) = 4–5 s	Major limitation: rapid regrowth of the tumor
Schwarzmaier et al. 2006 [36]	Glioblastoma (16)	>20 mm	Diffuser tip	P = 6 W	Overall survival longer than those reported from natural history or after chemotherapy
Streitparth et al., 2009 [37]	Osteoid osteoma (1)	5 mm	Bare fiber	P = 2.3 W t = 11 min	—
Dick et al., 2002 [38]	Renal tumor (9)	—	Cooled Bare fiber	P = 25 W t = 10–30 min	Two minor and one major complications
Di Matteo et al. 2013 [39]	Neuroendocrine Pancreatic tumor (1)	—	Bare fiber	P = 4 W t = 5 min	—
Mauri et al., 2016 [40]	cervical lymph node met (24)	—	—	1 or 2 fibers, P = 3–4 W t = 5–10 min	No major complications; 2 minor complications (8.3%).

Hepatocellular carcinoma (HCC) and liver metastases were the most commonly treated cancers by Nd:YAG lasers. These treatments are performed with low power, measured in Watts, and the time of treatment, measured in minutes (e.g., 5 W and 6–12 min [20]). Laser power can be increased to 30 W–40 W with cooled applicators [41]. Different groups used this laser for liver metastases [21] with good results in terms of survival rate and complications [23–26]. Large liver metastases have been treated with modified techniques consisting of "pull back" of the applicator or the use of multiple applicators [22].

Premalignant lesions and early stages of penile cancer carcinoma have been treated since the 1980s. The indication for the use of LA in this clinical setting is superficial penile cancer (either Tis or T1 disease). Contraindications to laser therapy include tumors with >6 mm depth invasion and T2 tumors [42]. Recently several studies focused on the efficacy of Nd:YAG lasers on penile cancer [29,30] and on the combination of Nd:YAG and CO_2 lasers [27,28], with good results in terms of local recurrence and satisfaction after the treatment, as well as good functional and cosmetic outcomes [27,43].

During the 1980s and 1990s, bladder cancer was treated by Nd:YAG lasers with high power and short time pulses [31,33,34,44]. The main risk is the perforation of the bowel or bladder [45], in particular at high laser power (>50 W) [46], although this has also been reported at 35 W [32]. This laser has been also used for the ablation of cervical lymph node metastases from papillary thyroid carcinoma with good results in terms of technical success (100% of the lymph nodes) and on complications (there were no major complications) [40]. Despite promising results, the use of Nd:YAG lasers on the treatment of bladder cancer has been abandoned, with the introduction of alternative lasers (see below).

Nd:YAG LA has been used as palliative treatments for several other cancers, e.g., colorectal [47,48], pancreas neuroendocrine tumors [39], lung [35,49], glioblastoma [36], osteoid osteoma [37], renal [38], ureteral tumors [50], and breast cancer [51]. These uses have generally been delivered at power settings of 5 W and a few minutes of application, or at high (50 W) power with short pulses of 1–3 s.

The Ho:YAG laser operates in pulsed mode at a wavelength of 2100 nm. Since the 1990s, it has replaced the Nd:YAG laser for the treatment of superficial bladder cancer [52,53]. Treatments are performed at different frequencies (5 Hz–40 Hz), energy per pulse (0.5 J–2.2 J), and power (4 W–40 W) [52–61], and show peri- and post-operative complication rates lower when compared to conventional transurethral resection (Table 2). In urology, this laser has also been employed to treat upper urinary tract tumors with settings similar to the ones employed during bladder ablation [62].

Table 2. Ho:YAG laser for tumor ablation (E= energy delivered by the treatment; P = laser power; f = frequency of the pulse).

Author	Tumor (Number of Patients)	Diameter of Tumor	Applicator	Laser Settings	Follow Up/ Complications
Syed et al., 2001 [55]	Bladder (41)	<1 cm	Bare fiber	E = 0.5–1.0 J f = 5–10 Hz	No complications
Razvi et al., 1995 [53]	Bladder (25)	<1 cm	Bare fiber	E = 0.5–1.0 J P = 4–7.2 W f = 8–14 Hz	No complications
Das et al., 1998 [56]	Bladder (23)	—	Bare fiber	—	1× recatheterization
Johnson, 1994 [52]	Bladder (15)	2–15 mm	Bare fiber	E = 1 J P = 10 W f = 10 Hz	No complications
Jonler et al., 2004 [57]	Bladder (52)	2–30 mm	Bare fiber	E = 1 J P = 40 W f = 40 Hz	Recurrence
Hossain et al., 005 [58]	Bladder (30)	<40 mm	Bare fiber	E = 0.5–1.2 J f = 10–12 Hz	Recurrence

Table 2. *Cont.*

Author	Tumor (Number of Patients)	Diameter of Tumor	Applicator	Laser Settings	Follow Up/ Complications
Zhu et al., 2008 [59]	Bladder (101)	—	Bare fiber	E = 1.5–2.2 J P = 20–40 W f = 15–20 Hz	—
Xishuang et al., 008 [61]	Bladder (64)	—	Bare fiber	E = 1.5 J P = 30 W f = 20 Hz	—
Wong et al., 2013 [60]	Bladder (54)	<30 mm	Bare fiber	E = 0.6–0.8 J f = 10–15 Hz	Recurrence
Matsuoka et al., 2003 [62]	Upper urinary tract (30)	5–30 mm	Bare fiber	E = 0.5–1 J P = 15–40 W f = 5–20 Hz	Recurrence

Laser diodes are replacing the Nd:YAG laser because they are more compact and portable (weighting less than 10 kg), less expensive, and deliver wavelengths between 800 nm and 980 nm with tissue penetration similar to that obtained by Nd:YAG lasers. Diode lasers have been largely employed on prostatic tumors with very good results in terms of complications and tumor recurrence (Table 3). The treatment is performed at different wavelengths (805 nm, 830 nm, or 980 nm) and the amount of damaged tissue is controlled with ultrasound, with temperature monitoring by fluoroptic thermal probes [63–65].

Table 3. Diode laser for tumor ablation (met = metastases; P = laser power; t = treatment time).

Author	Tumor (Number of Patients)	Diameter of Tumor	Applicator	Laser Settings	Follow Up/ Complications
Atri et al., 2009 [65]	Prostatic carcinoma (1)	16 mm	1 bare fiber	Two lasers at P = 15–2 W, t = 12 min	Necrotic tissue in targeted area
Amin et al., 1993 [64]	Prostatic carcinoma (1)	—	3 applicators	P = 2 W t = 500 s	Biopsies confirmed the presence of necrosis
Linder et al., 2009[63]	Prostatic carcinoma (12)	—	1 or 2 applicators	—	67% of patients free of tumor in the target at 6 m
Gangi et al., 2007 [66]	Osteoid osteoma (114)	<24 mm	Bare fiber	P = 2 W t $\leq$ 600 s	6 recurrence, 1 unsuccessful treatment
Carpentier et al., 2008 [67]	Metastatic intracranial tumor (4)	<3 cm	Light-diffusing tip	P = 15 W	No tumor recurrence
Dowlatshahi et al., 2002 [68]	Breast tumor (54)	5–23 mm	—	P = 5 W	Complete destruction of 93% of the tumors
Haraldsdóttir et al., 2008 [69]	Breast tumor (54)	—	Bare fiber	P = 3 W	Small skin necrosis in two patients
Gillams et al., 2000 [70]	Hepatic met (69)	—	Bare fiber	P = 2–2.7 W for each fiber t = 440 s	LA improves survival in patients with inoperable but limited liver met.

Laser diodes (980 nm) have also been used for metastatic brain tumors using a temperature feedback obtained by MR (Magnetic Resonance)-based thermometry, with reasonable preliminary results on four patients in terms of both tumor recurrence and complications [67]. Osteoid osteoma has been treated by a diode laser (805 nm) with good results in terms of recurrence (only six recurrences in a cohort of 114 patients and all were treated successfully with a second application) [66]. Because of the increasing detection of small breast cancer due to the widespread use of mammography, the diode laser (805 nm) is also being investigated for the treatment of small tumors with the use of temperature feedback [68,69]. It is also being explored for the treatment of hepatic metastases from colorectal cancer using a wavelength of 810 nm [70].

4. New Solutions to Guide Laser Ablation

The most promising emerging solutions in terms of the potential clinical impact on LA aim at controlling with high accuracy the amount of damaged tissue or at obtaining a more selective tumor

treatment that does not damage the surrounding healthy tissue. Recent efforts are devoted to the development of Hyperthermal Treatment Planning (HTP) tools, to the improvement of new solutions for real time thermometry, and to the use of tumor targeted nanoparticles. In this section, the basis and the most significant challenges of these three promising solutions will be described.

HTP tools aim at establishing the treatment settings that maximize the thermal treatment quality. HTPs model the interaction between the energy delivered by the thermal treatment and the tissue, in order to obtain a prediction of the tissue temperature distribution and therefore the amount of damaged tissue volume. As described in [71], the simulations can be divided in three main steps: (1) the first step is the generation of the patient model. This is aimed at obtaining a description of the geometry and of the physical properties of the tissue undergoing the treatment. This first step is crucial because the geometry and characteristics of the tissue strongly influence the interaction between the tissue and the energy delivered to treat the tumor (i.e., laser light in the case of LA treatment); (2) the second step is focused on the calculation of the amount of power absorbed by the tissue. Obviously the models employed depend on the kind of device used to induce the hyperthermia. In LA, the simulation is aimed at calculating the light distribution within the tissue. This task is usually performed using the Monte Carlo simulation and requires the knowledge of the tissue optical properties at the used laser wavelength and the emission modality of the applicator; (3) the third step provides the tissue temperature distribution. The model most widely used to perform this prediction is the Pennes' equation. The accurate prediction of temperature can improve the treatment outcomes.

The importance of HTP (hyperthermal treatment planning) tools in current clinical settings is confirmed by the recent decision of the European Society for Hyperthermic Oncology to include HTP in their quality assurance guidelines for deep hyperthermia [72], and by the recent development of several commercial treatment planning packages (e.g., the Sigma -Hyperplan system, VEDO, Semcad X, and Alba HTPS) and flexible software packages [73,74]. HTP tools have been clinically evaluated and validated [75,76]. Recently, Hyperplan predicted both the occurrence of discomfort and its location in a cohort of 30 patients with an error of the temperature prediction lower than 4 °C [77]. HTP tools have been also used for improving the safety and effectiveness of local hyperthermal treatments combined with radiotherapy and chemotherapy [78,79]. In spite of the HTPs limitations in the accurate prediction of the temperature distribution, they have demonstrated marked improvements over the last few years, so their integration into the clinical workflow is gaining acceptance [80]. In addition, temperature feedback obtained by thermometric techniques could correct HTP prediction during the treatment.

The importance of temperature monitoring during LA can be motivated by considering that the amount of damaged tissue depends on both the tissue temperature map and the exposure time [81]; therefore the knowledge in real time of the tissue temperature may be particularly beneficial for the optimization of laser settings applied during treatment. Thermometric techniques can be divided in two categories: invasive techniques and non-invasive techniques [82].

Among the invasive thermometric techniques, the most largely employed transducers are thermistors, thermocouples, and fiber optic-based sensors. Their use has been investigated in many recent in vivo and ex vivo cancer thermal treatment studies [83–86] and on different organs [87,88]. They allow for real time temperature monitoring with good spatial resolution, and quite good (thermocouples) or good (thermistors) accuracy. Their main drawbacks are related to their intrinsic invasiveness, and measurement only at a single point. There can also be measurement errors due to the strong light absorption of the wires of the thermocouple [89–91] and due to the high heat conduction for both thermocouples and thermistors.

Two kinds of transducers based on fiber optic technology are employed in this field: Fiber Bragg Grating (FBG) sensors and fluoroptic sensors. These sensors have been introduced in this field more recently than thermocouples and thermistor [63,92,93]. Their main advantages are related to due to their immunity from electromagnetic fields and their MR-compatibility, which allows for using this sensor during MR-guided procedures [94]. Their small size and flexibility, short response time, good

spatial resolution, and good accuracy (≈0.2 °C) are also assets. Their main drawbacks are related to their invasiveness, and measurement only at a single point for flouroptic sensors. Moreover, FBGs are sensitive to the strain that can produce measurement errors during in vivo trials caused by the respiratory movements of the patients [95]. Temperature probes embedding FBGs within a needle have been proposed to tackle this problem [96,97]. Regarding the fluoroptic sensor, the error caused by laser light absorption cannot be considered as negligible [91].

The most promising non-invasive thermometric methods are MR-based thermometry and CT (Computed Tomography)-based thermometry.

Basically, MR-thermometry is founded on the dependence of a number of MR parameters on temperature [98]. After a series of experiments on phantoms, ex vivo tissues, and on in vivo animal models [99], MR thermometry has been employed during LA of HCC and liver tumors , prostate cancer, and metastases during the last decade [100–102]. Recent studies have shown the possibility of obtaining good spatial and temporal resolution and good precision [103].

CT-thermometry was first investigated during the 1970s [104], but investigations were discouraged by the limitation of the CT scan in terms of reproducibility and stability. In the last decade, the improvements of CT scanners have encouraged a number of groups to use this method in thermal treatment. During the last few years this technique has been mainly employed during ex vivo experiments and on phantoms [105–110]. Although laser ablation guided by non-invasive thermometry is in its infancy, recent technical solutions are helping to increase the number of studies in animal models and in humans.

The main advantages of these two non-invasive techniques are related to the non-invasiveness and to the possibility of obtaining a tridimensional temperature distribution. The main disadvantages of MR-thermometry are related to the cost of the MR scan, cost of custom made sequences to obtain good thermal sensitivity, and the hazards of working in an MR environment; the main drawback of the CT-based thermometry is related to the use of ionizing radiation.

Finally, an emerging solution which is noteworthy is the use of nanoparticles in the photothermal ablation of cancer. The aim of this solution is to improve the selectivity of the treatment in order to destroy the tumor while preserving the integrity of the healthy surrounding tissue. The basis of this therapy is that materials that highly absorb light can be designed and delivered specifically to the tumor cells. The subsequent application of light will then cause specific thermal killing to nanoparticle tagged tumor cells.

Gold based nanoparticles have been designed and absorb light in the near-infrared (NIR) region where water and hemoglobin show high transmissivity (as shown in Figure 2). If the nanoparticles are selectively accumulated in the tumor, the light will be mostly absorbed by the tumor only. As a consequence, the absorbed light that is converted into heat energy causes a temperature increase localized in the target. This specificity depends on the geometry, morphology, and surface charge of the nanoparticles; therefore several kinds of gold nanoparticles have been designed for photothermal ablation to optimize the absorption and selectivity (e.g., nanorods, nanoshells, branched nanoparticles, and nanocages) [111]. These nanoparticles have been used in several cancer models (e.g., breast cancer, pancreatic cancer) [112–114]. The comparison between the effects on cells in the absence of nanoparticles and on cells with nanoparticles has been performed to assess the efficacy of this technique [112,115]. For instance, El-Sayed et al. noted that in the absence of nanoparticles, the cells did not experience destruction up to a laser power density of 76 W/cm^2; on the other hand, benign cells with nanoparticles were destroyed at 57 W/cm^2, and for malignant cells it occurred at a lower value (25 W/cm^2) [116]. Recently, this technique has been evaluated in vivo in animal models. The efficacy of in vivo treatment has correlated to the findings that nanoshell-treated tumors were noted to experience a temperature increase higher than that for the nanoshell-free controls (37.4 ± 6.6 °C vs. 9.1 ± 4.7 °C) [117].

Clearly, the use of nanoparticles in this treatment approach is in its infancy. The early promising results bring expectations that this approach may have an important future clinical impact. Further

improvements and successful introduction in therapy require a proper evaluation and understanding of their interactions with biological entities and their potential for inadvertent toxicities [118,119].

5. Discussion

LA is becoming a valid alternative to surgical resection. The ultimate goal of LA is to reduce the suffering related to specific cancers and to improve outcomes. After the tumor localization and the identification of its features (geometry, contours, histology), there are two main challenges in LA: an accurate placement of the applicator in the tumor, and accurate treatment planning and monitoring. New HTP tools and monitoring tools are beginning to overcome some of these challenges, and they are gaining widespread attention and broad clinical acceptance as techniques for improving the safety and outcomes of thermal treatments.

The current landscape of LA is changing rapidly, with new and exciting developments. Among others, emerging solutions and developments which are noteworthy are: the recent evolution in the use of new lasers with different wavelengths and modes of operation, and equipment (e.g., custom applicators) are leading to promising results in terms of treatment selectivity; the improved understanding of the laser-tissue interactions is used to increase the accuracy of computational models for HTP tools for planning patient-specific treatments; the improvement in precision and accuracy of tridimensional non-invasive thermometry and the increasing interest in multi-point temperature probes based on FBG technology are gaining widespread attention for the real time monitoring of the effects of LA; and lastly, the progress in targeting nanoparticles to tumor cells as well as the possibility to specifically tune the laser to the surface plasmon resonance frequency of the nanoparticles are paving the way for the advent of targeted heating. For the promise of this technology to be realized, new solutions, such as HTP tools, thermometry, and the advancement of nanotechnology in medicine, have to be further improved and translated for clinical use. This requires a continued and close research collaboration between interdisciplinary groups involving clinical experts, physicists, bioengineering, and material scientists.

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