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THERALIGHT

Lightwave Technologies for Theranostic of Tumors

Executive summary

Thermal Ablation (TA) is a class of interventional techniques that deploy electromagnetic energy sources to treat malignant diseases by inducing thermal damage and, eventually, coagulation necrosis in tissues. Among similar techniques, laser thermal ablation (LTA) stands out as particularly promising due to a number of factors:

- it can be used in combination with many different imaging systems (such as ultrasounds, computerized tomography and magnetic resonance);
- the optic fibers can be designed to fit the double function of energy delivery and temperature sensing;
- the probe it uses in order to reach the area to be ablated has a small diameter, that allows for its use also in tissues at high risk of damage;
- it is economically convenient with respect to similar technologies.

The main limitations of LTA, however, are the restricted dimensions of the area ablated with a single fiber and the technical complexity of manually inserting the probe.

Theralight project aims at identifying a novel concept capable of overcoming the current LTA limitations.

The solution entails the following aspects:

- redesign of the probe handling system, to support surgeons during the insertion procedure to reach the tumor mass with the utmost accuracy;
- research of alternative biocompatible materials for the probe, to further reduce the cost of the instrumentation and, consequently, facilitate its adoption in clinical practice. Due to its flexibility, transparency, and resistance, polycarbonate was selected as the most suitable material for the probe, while polypropylene well performs the functions associated to the handling;
- introduction of alternative and sophisticated temperature monitoring techniques that could provide a more accurate feedback, in real time, on the outcome of the procedure. The fluorescence sensing and mapping system is demonstrated as a promising approach to the temperature monitoring in real time during LTA procedures;
- design of Virtual Reality training systems for encouraging surgeons to adopt LTA (which is currently not as used as it should be).

The ensemble of these solutions can breed a new generation of LTA tools that could become an important alternative to traditional surgical resection.

Key Words

“Laser Thermal Ablation”, “Tumor Theranostic”, “Temperature Monitoring”, “Biocompatible Materials”, “Probe Design”

Project description written by the Principal Academic Tutor

LTA is a powerful minimally-invasive treatment with high potential, but so far with limited clinical use for its novelty and the lack of tools for patient-specific treatment.

With the aim of providing a contribution to help overcoming current limitations, THERALIGHT will analyze novel strategies for laser-based theranostric of cancer by combining patient-specific beam delivery solutions and advanced monitoring techniques. Following the design of an innovative LA system, lab tests with phantoms and ex-vivo trials will allow the team to validate the proposed solutions and to drive the possible workflow re-design. Then, the most promising solution will have the possibility to be tested in a practical environment to assess its impact in practical cases of tumor ablation.

In more detail, the project will consist of five phases, with three of them partially overlapped:

- Review of the state-of-the-art (All – M1-M3): analysis of the literature and of other ongoing research projects (e.g., European funded projects) to become familiar with laser ablation procedures.
- Identification of requirements (Sub-team A – M4-M10): interaction with possible end-users (mainly surgeons) to identify the needs and to carry out preliminary assessments of the relevance (and acceptance) of the innovative aspects; definition of the regulatory framework for the medical device developed by the team.
- Development of new prototypes (Sub-team B – M4-M10): study of the applicators that embed two different functions: laser light delivery and process outcome measurement (mainly through the evaluation of the temperature field during the LA procedure). Different light emission patterns and laser wavelengths will be investigated with the goal of adapting the shape and size of the treatment affected region to the tumor lesion. The measured temperature values will be processed and used to represent and visualize in real time the evolution of the ablation volume, with the aim to provide the clinician with a visual feedback of the LA outcome. The possible development of magnetic-resonance (MR) compliant needles to allow the percutaneous insertion of the applicators under MR procedures will be considered as well.
- Preliminary lab tests (All – M7-M10): metrological assessment of the sensors, preliminary tests in tissue-mimicking phantoms, and validation of the platform for the real-time visualization of measured temperature values.
- Final assessments (All – M11-M15): final ex-vivo and in-vivo trials to validate the devices and the workflow in simulated clinical scenario, data analysis, demonstration to end-users and survey to evaluate the usability of the tool, preparation of conclusive reports.

Team description by skill

Chiara Bregoli: her Biomedical Engineering expertise with a specialization in biomechanics she contributed with her skills in biomechanics and biomaterials analysis at the design of the LTA instrumentation, focusing both on device's structure and suitable materials research.

Federica Buccino: with her Biomedical Engineering expertise with a specialization in biomechanics she contributed with her skills in biomechanics and biomaterials selection at the design of the instrumentation, both as morphology and as materials composition.

Chiara Coletti: with her Biomedical Engineering expertise with a specialization in electronic technologies she contributed with her skills in signal and image processing and radiation physics at the research for temperature monitoring techniques, sensing and controlling principles and imaging.

Chiara Di Vece: with her Biomedical Engineering expertise with a specialization in electronic technologies she contributed with her skills in signal and image processing, sensors and computer-aided surgery at the research for temperature monitoring techniques, sensing and controlling principles and virtual reality developments.

Davide Manzionna: with his Management Engineering expertise he contributed with his skills in product industrialization at the research for the product value and positioning inside its reference market, as well as the practical economic feasibility of the proposed solutions.

Elena Hilary Rondoni: with her Biomedical Engineering expertise with a specialization in electronic technologies she contributed with her skills in biotechnology, radiation physics and medical imaging at the research for temperature monitoring techniques, sensing and controlling principles and imaging.

Antonio Sindoni: thanks to his Mechanical Engineering expertise, he contributed with his skills in Designing for Additive Manufacturing and 3D printing optimization at studying new solutions for the main tools regarding LTA, realizing also the 3D functional prototypes of two different probes.

Luca Viale: with his Mechanical Engineering expertise he contributed with his skills in design and automation at the design of the instrumentation, both as morphology and materials composition.

Goal

THERALIGHT project aims at identifying a novel design concept capable of overcoming the current limitations in LTA and, as a result, promote its use for the minimally invasive treatment of lesions from solid tumors.

The design of a theranostic tool, able to perform laser ablation of soft tissue with real-time process outcome monitoring capabilities, needs to be carried out following two parallel, but communicating, research lines, from the early state-of-the-art study until the latest developments. As already seen in the team composition, the objective of this project must be pursued both in the field of electronic with the research for temperature monitoring techniques, sensing and controlling principles, and in the biomechanic one with the study of the design of the instrumentation, in terms of morphology and materials composition.

The importance of these results is not limited to the external institutions involved in the project – actually, they can be considered more "support institutions" than stakeholders – but they could give benefits to the entire society if a reduction of the mortality rate of very aggressive tumors (an example for all, pancreatic cancer) can be successfully achieved. Moreover, the developed procedure could even have a stronger impact as it could be extended to other fields of medicine, such as in the ablation of obstructed blood vessels, brain lesions, etc.

Understanding the problem

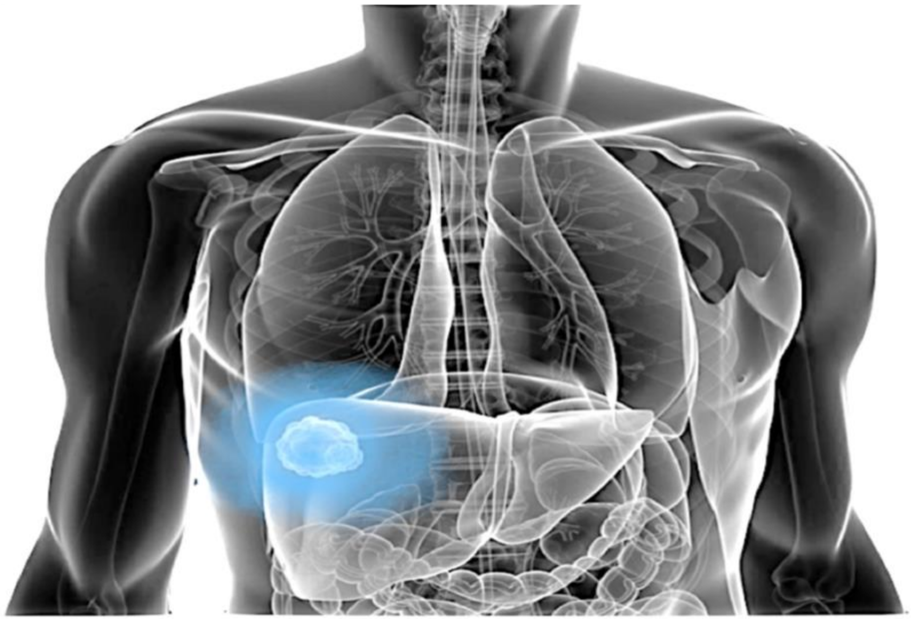
"Those diseases which iron cannot cure, fire cures".

Hyppocrates' quote introduces the paradigma behind thermal ablation (TA) techniques.

It refers to the destruction of tissue by extreme hyperthermia. The TA techniques have been introduced as alternatives to classic surgical resection only in the second half of 1900 and are still being developed. The working principle of this technology is to deploy electromagnetic energy sources, such as radiofrequencies, microwave or laser to induce thermal damage and, eventually, coagulation necrosis in tissues and treat malignant diseases.

The key feature of TA is that it turns out to be a less invasive solution with respect to traditional surgery; in addition, sometimes, this is the only way to proceed when a traditional approach is not feasible to cure certain tumors. Indeed, TA can be performed using an open, laparoscopic, or endoscopic approach. Operation lasts about 10-30 minutes and, even if it is different from a classical surgical operation, anesthesia is generally used. For most cell types, necrosis occurs at temperatures below -40 °C or in excess of 60 °C.

Laser Thermal ablation (LTA), in particular, has the peculiarity of being MRI-compatible, allowing also for temperature mapping, since energy is conveyed through optic fibers; it is economically convenient with respect to the other TA technologies and the small diameter of the probe allows for its use also in tissues at higher risk of damage. Furthermore, the fiber used to deliver the treating light can also be used to collect information on the temperature and, thus, combine therapeutic and diagnostic functionalities, unlike any other thermal ablation technology. The main limitation of LTA, however, are the restricted dimensions of the ablated area with a single fiber, due to the high absorption of light by body tissues, and the technical complexity in the manual insertion of the probe. These factors require the adoption of several strategies to facilitate the interventional procedure and increase energy penetration.

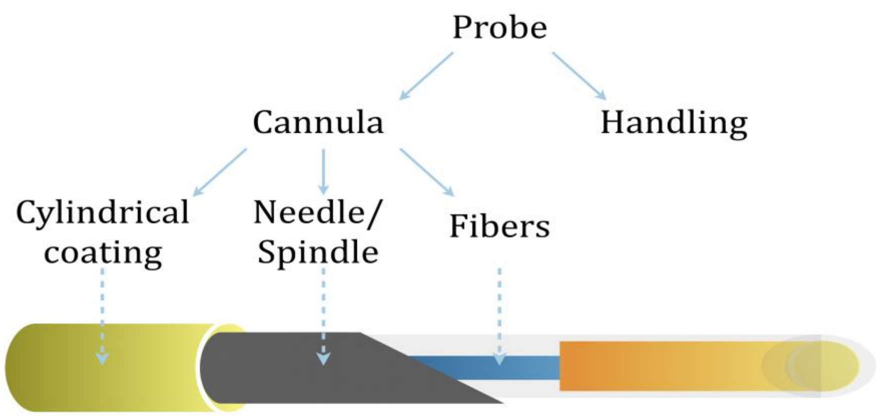


Considering the strengths and weaknesses of LTA, the final goal is to make this treatment possible and affordable for a larger amount of people. In this project, in particular, the first phase has been dedicated to the analysis of the state-of-the-art in order to prepare a significative questionnaire to be given to the surgeons. The comprehension of the answers and the analysis of different suggestions, led to the second phase, more focused on the concept of the new device. The 3D prototype derives both from the surgeons' observation and Theralight team's researches and studies. This third phase is completed by the feasibility analysis which includes the research of the sensors and the materials and the analysis of different competitive techniques in order to make the proposal cutting-edge on the market.

Exploring the opportunities

As mentioned before, starting from the researches related to the laser interaction with different human tissues, the need for water injection and mechanical guidance during the treatment to better control the process, we tried to understand in details the structural composition of the whole real systems with needles and probes as leading sub-systems, as shown in the figure below.

Subsequently, the surveys given to the surgeons helped us to solve the main issues related to current laser ablation devices, to explore the foremost needs of the stakeholders and to translate them into specific requirements. The surveys aimed at collecting as much data as possible from previous experiences of surgeons, who have already performed interventions with laser ablation systems, in order to identify strengths and possible improvements to make this technique even more efficient and advanced. The opinions of the majority of the physicians focuses on the minimally invasiveness of the considered technique, on the reduction of the post-operative complications and of the convalescence period, on the higher tolerability, also in high-risk patients, and on the reduced dimensions of the probe (2,5 mm in diameter). However, what is perceived as a limiting factor for the diffusion of LTA practice, is basically the adoption of LTA by the hosting structure and the novelty of the technique, that implies the necessity to introduce more specific - and expensive - training for LTA.



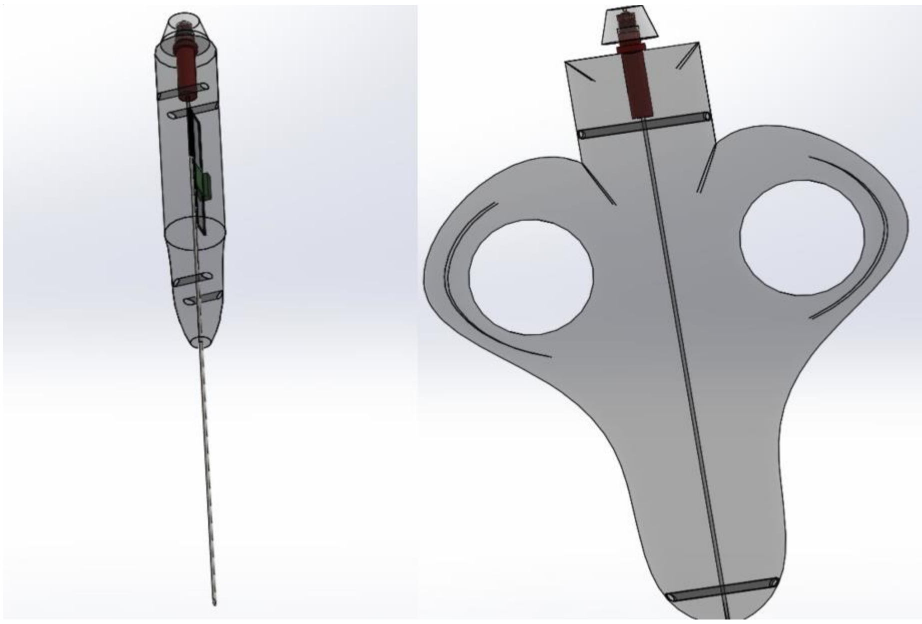
Representation of the structural composition of the whole system. The needle and the probe are considered as leading sub-systems.

According to the interviewed physicians, one aspect that turned out is the necessity for a LTA probe improvement: the reliability of the measurements and the completeness in monitoring temperature parameters seem to be the most urgent features to be revised. The necessity to perform a control on the distribution of the temperatures in the periphery of the ablation zone, in order to avoid damages on the contiguous vital structures, has been highlighted by most of the surgeons. Another relevant improvement should be performed in the reduction of probe fragility. For these reasons, a re-design of the LTA tool was performed.

The selected price (economical requirements) for the whole LTA instrumentation should range from 500 to 1000 €: this is one of the key parameters that must be considered in the implementation of an improved device since the commercialized ones are considered too expensive.

Generating a solution

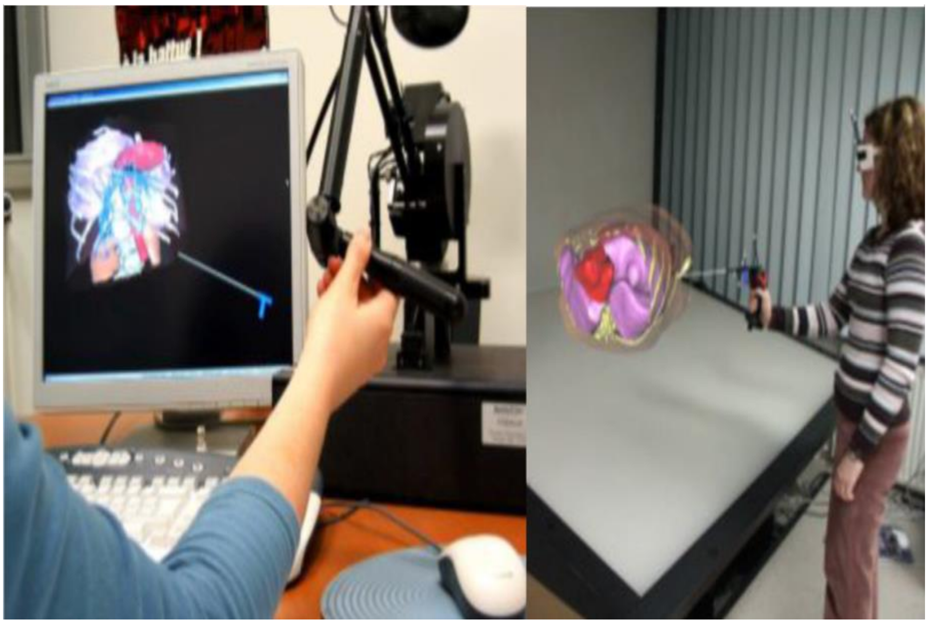
Some issues and concerns have arisen from the study of surgeons' opinions and LTA system components. The objective of this work is to tackle them, mainly from two different perspectives. The first one regards the research done in terms of best materials to be used for probe fabrication. They must respond to precise requirements dictated by mechanical properties that the device should present. Moreover, a new design for the handling portion of the probe itself is proposed. The second one focuses on the necessity of finding evermore precise implementations for the monitoring system. In particular, a novel solution, that uses fluorescence is proposed. According to the devices already available and the suggestions expressed by the interviewed surgeons, a transparent, quite flexible and resistant polymeric material may be the right choice for the probe. It is possible to state that polycarbonate could be a good material for this purpose. For the same reasons, polypropylene with a possibility of an anti-slip silicone covering was chosen for the handling, in order to increase the manageability and to avoid uncomfortable surfaces. Moreover, regarding the handling, it turned out from the survey that many surgeons have complained about the absence of ergonomic features. This is the reason why the Theralight team have tried to generate a prototype through 3D printing able to give some useful indications. The type of prototype, shown in the figure below, is a conceptual one, i.e., only aimed at verifying the idea. Giving a brief description, the first is thinner with a tubular structure. On the other hand, the second allows surgeon to firmly keep the device inserting fingers in the two holes. The tubular handling could also be provided with a system able to customize and change the length of the fibers in order to fit perfectly the purpose for which it is using.



Conceptual prototype of the handling portion of the probe generated through 3D printing. The first one on the left is thinner and presents a tabular structure, whereas the one on the right allows the surgeon to keep more firmly the device since he or she is able to insert the fingers in the holes.

Regarding the sensors monitoring study, instead, the fluorescence sensing for laser ablation monitoring has proven to be a promising technique, even though it is at its primordial stages and it is still limited to experimental studies. Its main limitations are the background noise, caused by the tissues autofluorescence, and the photobleaching process, in which the emission is reduced due to chemical degradation of the fluorophores. For what concerns the noise, possible alternatives have been studied, such as the exploitation of the Förster resonance energy transfer mechanism to absorb the background emission, hence used as an excitation source. To deal with photobleaching, ratiometric measurements may be a possible solution.

In conclusion, since LTA is not commonly carried out yet, also because the success of the intervention strongly depends on the skill level of the operator, it was suggested that virtual and augmented reality simulators could represent the key to progress, allowing trainees to be able to cope better and with less stress with the intraoperative situations of real life. These tools could be used to train the next generation of surgeons specialized in TA.



Examples of simulators that could be effective in order to train the next generation of surgeons specialized in TA. Virtual reality in particular could be useful for the development of surgical simulators in order to train and improve the acquisition of the necessary psychomotor skills.

Main bibliographic references

C. M. Pacella, G. Bizzarri, G. Francica, A. Bianchini, S. De Nuntis, S. Pacella, A. Crescenzi, S. Taccogna, G. Forlini, Z. Rossi, et al., *Percutaneous laser ablation in the treatment of hepatocellular carcinoma with small tumors: Analysis of factors affecting the achievement of tumor necrosis*, Journal of vascular and interventional radiology, vol. 16, no. 11, pp. 1447–1457, 2005.

S. N. Goldberg, G. S. Gazelle, and P. R. Mueller, *Thermal ablation therapy for focal malignancy: A unified approach to underlying principles, techniques, and diagnostic imaging guidance*, American Journal of Roentgenology, vol. 174, no. 2, pp. 323–331, 2000.

D. J. Webb, M. Hathaway, D. A. Jackson, S. Jones, L. Zhang, and I. Bennion, *First in-vivo trials of a fiber bragg grating based temperature profiling system*, Journal of biomedical optics, vol. 5, no. 1, pp. 45–51, 2000.