Recherche Hospitalo-Universitaire – 3ème Vague

Rapport scientifique à mi-parcours

destiné aux membres du jury international

Perfuse

Projet ANR- 17-RHUS-0006

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A. PROJECT PROGRESSION

1 SCIENTIFIC SUMMARY OF THE RESULTS OBTAINED SINCE THE BEGINNING OF THE PROJECT

Work Package 1: assessment of F-HIFU therapy

Task 1.1: HIFUSA, multicenter F-HIFU phase III study for low risk patients

HIFUSA is a randomized, multicenter study (14 centers) comparing 2 groups of patients with significant Gleason 6 single cancer foci:
- Focal-High Intensity Focalized Ultrasound (F-HIFU);
- Active surveillance.

As Fig. 1 shows, the recruitment of patients started in October 2018.

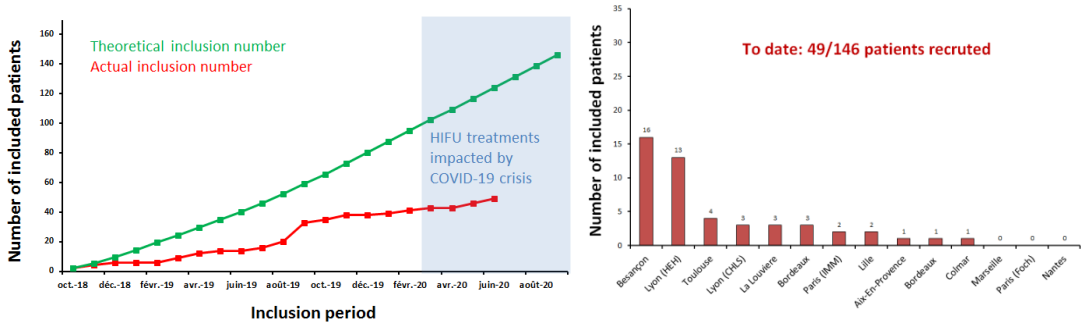

Fig 1: Theoretical and actual HIFUSA inclusion curves (left); patients included in each clinical center (right).

As the main endpoint of this study is the proportion of patients with conversion toward additional focal or radical treatment after 4 years, scientific results are not available yet.

Task 1.2: FOCALE, multicenter F-HIFU phase II study for intermediate risk patients

FOCALE is a prospective, multicenter (14 centers) trial evaluating F-HIFU for patients with a Gleason 7 (3+4) single cancer focus. Inclusions started in October 2018 (Fig. 2). As discussed above, scientific results are not available since the main objective of this study is evaluated 2 years after the F-HIFU treatment.

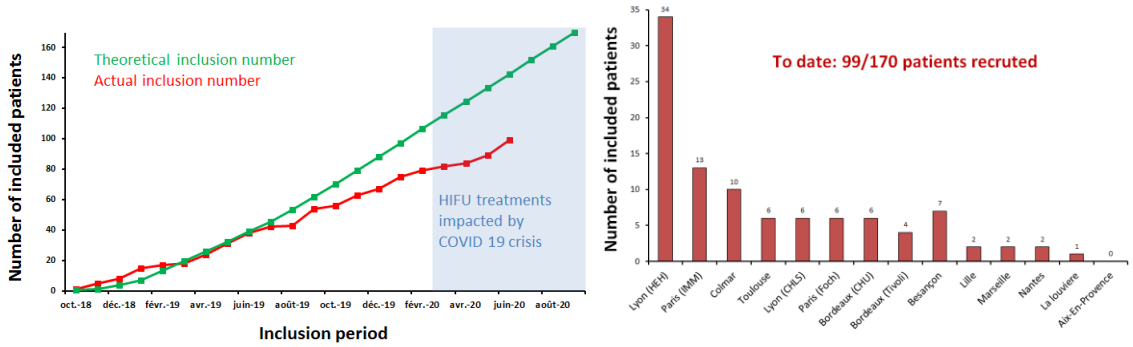

Fig 2: Theoretical and actual FOCALE inclusion curves (left); patients included in each clinical center (right).

Task 1.3: Salvage F -HIFU treatment with PSMA-PET-MRI guidance after EBRT failure

A pilot study was setup to evaluate the use of PSMA-based IRM-PET to guide Salvage-Focal-HIFU (SF-HIFU) with FocalOne® in patients with local prostate cancer recurrence without metastasis, after External Beam RadioTherapy (EBRT).

The trial was activated in March 2020 as a result of the collaboration between the Hospices Civils de Lyon (HCL), the CERMEP laboratory and the Centre Léon Bérard (CLB); the first patient was recruited in June 2020.

Task 1.4: "Ancillary" study, biological response evaluation

Hypothesis: HIFU-focal treatment will actively modulate the systemic immune response in prostate carcinoma patients either with intermediate risk (FOCALE study) or with recurrence after radiotherapy (PSMA study). To validate this hypothesis we performed the monitoring of phenotypic and functional modulations of immune cells in the blood of patients enrolled in the FOCALE clinical study on the site of Lyon (*Task 1.2*) at the time of inclusion and after one and three months. Before the beginning of the clinical trial, we set up and validated 14 colors flow cytometry panels on the Fortessa x20 (partially funded by the RHU) to investigate modulations induced by HIFU treatment on the phenotype (activation, immune checkpoint (ICP) expression, KIR/KAR expression, differentiation state, proliferation) of adaptive (T cells) and innate (monocytes, dendritic cells subsets, NK cells) immune cells. To date, 24 patients have been enrolled in the ancillary study and, in parallel, 20 healthy men have been recruited in a control cohort. Part of these samples were transformed into Peripheral Blood Mononuclear Cells (PBMC) and frozen in liquid nitrogen at the CLB institutional Biological Resource Center for subsequent analyses. The functional analysis will be performed after the last inclusion to reduce batch biases. The phenotypic analysis was performed by analyzing flow cytometry raw data for 17/24 patients with particular interest on T cells and NK cells. We notice short term modulations (comparing untreated and 24h treated patients) that return to basal levels after 1 month. The most significant observation is an increased number of white blood cells in all patients after 24h that is not always related to an increased T or NK cell number. We do not observe significant modulation in proliferation (Ki67) or state of differentiation of these T cells but we notice modulation in KIR/KAR expression by NK cells in several patients. At later time point (M1, M3), we observe an increase in ICP expressed by CD4 T cells (PD1, ICOS, CD39) but not on CD8 T cells except for TIGIT that is increased on CD8 T cells in several patients at M3. The analysis of DC and monocyte subsets is currently in progress. These results have to be compared with those of healthy donors and also to be related with efficacy of the HIFU treatment, clinical data at inclusion as well as other parameters analyzed (CTC, PCA3 levels in urine) to explain the different modifications observed that are not detected in all patients.

Work Package 2: diagnosis of prostate cancer foci

Task 2.1.1: Collaborative computer-based database

In order to gather the MRI exams from the different hospitals but also to make the centralized database available to our targeted collaborators, we setup a specific open source imaging informatics platform: the XNAT server (Neuroinformatics Research Group, Washington University). This XNAT server is installed within the HCL secured datacenter and can be accessed via a secured webpage (login and password required) from the internet. The entire HCL radiological pathological correlation CLARA-P database (290 patients with prostatectomy whole-mounts and pre-operative annotated MRIs) has been uploaded and made available to LabTAU and Creatis for Tasks 2.1.2 and 2.1.3.

Task 2.1.2: Creation of a quantitative CAD system

The HCL and LabTAU had already designed a preliminary Computer Aided Diagnosis (CAD) system at the start of the PERFUSE project. This CAD used only two simple image parameters and had shown robust performance at internal validation for detecting ISUP ≥2 prostate cancers (**Dinh et al. 2016; Dinh et al. 2018**).

This preliminary CAD was therefore tested on an external dataset of multiparametric MRIs obtained in patients who underwent prostatectomy, as planned in the "PARIS" study of the PERFUSE programme. Initially, the MRIs should have been provided by the Hôpital Pitié-Salpétrière in Paris, but unfortunately we could not have the corresponding histological prostatectomy. Therefore, the study was made on a dataset from Dijon University Hospital. The MRIs were interpreted by an experienced radiologist (>20 years experience) who assessed a PI-RADSv2 score to all visible lesions and the results of human reading were compared to those of the CAD. The CAD performed slightly better than the human expert for characterizing ISUP≥2 prostate cancers (AUC of 0.78 (95% confidence interval, 0.69-0.87) vs 0.74 (95% confidence interval, 0.62-0.82); p=0.59) (**Transin et al. 2019**).

More recently, the work on the CAD was carried on by a PhD student who completed the following tasks:
-CLARA-P database cleaning: checking the image quality and completeness of all MRI datasets; checking and correcting inaccuracies in positioning and labelling of regions of interest (ROIs) attached to MR images.
-Training a new ROI-based CAD on the entire CLARA-P database (290 patients).
-Testing the best CADs obtained from the training database in an intermediate multi-vendor database of 100 patients who underwent prostate MRI before biopsy (to further select the best models and define diagnostic thresholds).
-Evaluating three ROI-based CADs on another test multi-vendor database of 160 patients who underwent prostate MRI before biopsy (and different from those of the intermediate database). The best CAD slightly outperformed the PI-RADS score (non-significant difference), confirming the robustness of our approach.

TASK 2.1.3: Investigation of complementary Machine Learning Techniques

Based on the state-of-the-art in this domain, we proposed to address two challenges:
- To predict not only a presence/absence of cancer but also the degree of its aggressiveness. The binary prediction does not suffice for active surveillance of patients with low aggressiveness cancers or patients that could benefit from focal therapy. The main challenge for multi-class classification algorithms is that the different classes, corresponding here to the different levels of lesion aggressiveness, are highly correlated and interdependent.
- To develop a system whose performance generalize well with data potentially coming from different populations as can be encountered with imaging data pooled over different clinical centers (i.e., acquired on different MR scanners and/or with different sequences and parameters).
A Ph.D. student was recruited and performed the following tasks:
- Benchmarking of the existing deep neural network architectures for multi-class segmentation of prostate cancer lesions as well as prostate contours (peripheral and transition zones).
- Performance evaluation on a series of 50 patients.
- Contribution to the CLARA-P database cleaning (Task 2.1.1).
- Design of a novel deep supervised architecture with an attention model on prostate peripheral zone. Performance evaluation on a series of 98 patients compare well to state of the art performance (**Duran *et al*. 2020**, accepted for publication).

Task 2.1.4: Multicenter clinical evaluation

The "CHANGE" study will evaluate the best CAD(s) obtained in Tasks 2.1.2. and 2.1.3. in a prospective cohort of patients referred for MRI before prostate biopsy.

Initially, it was planned to perform a prospective multicenter study in which MR lesions would be defined first by human reading (PI-RADS score) and then by the CAD(s). Suspicious lesions would then be biopsied, the biopsy results being used as the standard of reference. However, it is estimated that the CHANGE study will take two years to be completed. It does not seem realistic to finish the development of the CAD(s) and complete the CHANGE study before the end of the program (November 2022). In addition, obtaining biopsies on the basis of CAD findings would need a CE marking which will induce further delays. As a result, an alternative design has been chosen (and validated by the PERFUSE Scientific Advisory Board) for the CHANGE study: a multicentre prospective cohort of patients with MRI and subsequent systematic and targeted biopsies (based on PI-RADS scoring) will be collected and will allow for a retrospective evaluation of the CAD(s). This new strategy will not allow assessing whether these CAD(s) can increase the sensitivity of cancer detection as compared to human reading, since lesions shown by the CAD and not by human reading will not be specifically biopsied. Nevertheless, a recent Cochrane meta-analysis has shown that the PI-RADS score has high sensitivity (0.91 [95% confidence interval, 0.83-0.95]) but very low specificity (0.37 [95% confidence interval, 0.22-0.38]) **(Drost et al. 2019).** Improvement due to CAD-assisted image interpretation is therefore expected to increase specificity rather than sensitivity. In addition, two measures have been taken to mitigate the risk of underestimating a possible increase in sensitivity due to CAD-assisted interpretation. First, patients will have systematic (random) biopsies of the gland in addition to biopsies targeting MR lesions defined by human reading. Second, a follow-up of three years is planned and the CAD results will be compared not only to the systematic and targeted biopsy performed just after the MRI, but also to the results of the three-year follow-up. The CHANGE study will assess the non-inferiority of the CAD(s) for detecting ISUP ≥2 cancers as compared to the PI-RADS 2.1 score (patients n=420). The study protocol will be submitted to an Ethics Committee at the end of June 2020. Recruitment should begin in the fourth quarter of 2020. The following centres accepted to participate: Lyon (HEH, CHLS, Hôpital Saint Joseph), Strasbourg, Lille, Saint-Etienne, Grenoble, Paris (Pitié-Salpétrière, Necker) Marseille (Hôpital Européen, Institut Paoli Calmette), Bordeaux, Nantes, Toulouse.

Task 2.2.1: MR Elastography for Prostate Cancer

We developed the MR-compatible vibrating device prototype, and successfully tested it in a 1.5T MRI on a phantom gel. We also implemented a new method for filtering out the compression wave that induces artefacts in MR elastography. An example is given in the figure below, which represents an elasticity image in a dual-layer object. Both layers are homogeneous. The artefact visible on the left ('no preprocessing') is removed with conventional methods resulting in a noisy image ('curl'), and successfully filtered with our newly developed technique ('shear only'). We are currently assessing the patentability of this method.

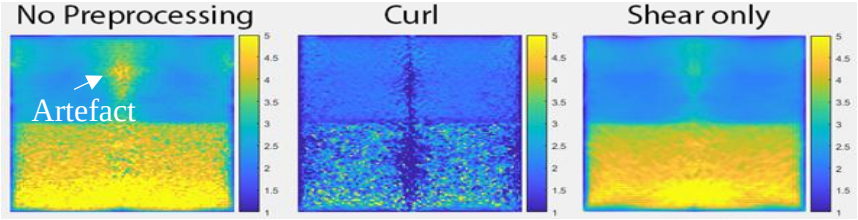

Fig 3: Simulated elasticity image of a dual-layer object with artefact due to the presence of compression waves (left), processed with conventional method (center) and newly in-house developed method (right).

Task 2.2.2: Passive elastography for HIFU lesions

Passive elastography is an ultrasound (US) technique which uses physiological vibrations, such as heart beat and artery pulsatility, as the source of the desired shear waves (**Catheline et al. 2013**). No external perturbation is required, thus the method can potentially assess the elasticity of any region provided that an adequate wave field is naturally present. The standard process of passive elastography consists in 3 steps:
- image acquisition of the targeted region (raw data at an ultrafast framerate (>500 Hz))
- signal processing via the displacement estimation technique;
- calculation of the shear wave speed based on this displacement field.

In order to implement the passive elastography technique into the FocalOne® system and eventually detect ablations, we performed simulations and experimentations in calibrated phantoms and bovine *ex vivo* liver. MRI 3D imaging was also performed for the *ex vivo* tissues to measure the ablated volume and compare with our results.

The BK Medical EB-2300 US scanner currently integrated in the FocalOne® does not provide access to the raw data needed for standard passive elastography. A roundabout was developed in order to use the available B-mode images in a modified passive elastography process. A novel method of displacement estimation, called GLUE (Global time-delay estimation in US Elastography; **Hashemi et al. 2017**), was implemented. Even though, a loss of resolution is apparent compared to the maps obtained with raw data, elasticity contrast is still clearly apparent. Preliminary tests have been performed on a euthanized pig with the ablation occurring in the liver through the caecum to mimic the rectum.

In parallel, a research system (Verasonics Vantage 256) was connected to the FocalOne® system and probe to acquire ultrafast raw data in tissue-mimicking phantoms and *ex vivo* liver samples. The shear waves had to be generated artificially in these models and several wave fields were tested for optimal results. Elasticity maps were obtained in *ex vivo* liver before and after FocalOne® ablation. Shear wave velocity increased by a factor 2.5 in average at the lesion foci. In addition, the detected region of increased stiffness correlated well with the ablation volume both planned on the FocalOne® and seen on MRI images.

Task 2.2.3: Clinical evaluation of Elastography

The study of the prostate MR elastography technique is progressing through administrative formalities for studies involving healthy volunteers.

Work Package 3: HIFU technical ruptures innovations

Task 3.1.1: Perfusion estimation of prostate tissue with pre-operative MRI

The objective is to investigate the relationships between intra-prostatic blood perfusion, treatment strategy and performance results by comparing simulation and clinical outcomes obtained retrospectively on 100 patients treated with the FocalOne® device.

<u>In silico study on the influence of perfusion</u>

An *in silico* study of perfusion-dependent sequences based on the RETRO clinical study was foreseen. Given the delay in the latter, however, we decided to dedicate this task to an *in silico* study of the influence of the perfusion on the tumor performance index using the "Fast-ABLASIM" research software (Report 1FCH20-0002). Several configurations corresponding to typical clinical cases and parameters of two sequences of FocalOne® device (STANDARD and OPTI) were simulated. In each configuration, the tumor was placed on the periphery of the prostate and the target was defined with a 9 mm margin around the tumor and limited to the prostatic capsule.

The simulations confirmed that an increase in blood perfusion can lead to a substantial drop in tumor performance index within the target volume. Importantly, the tumor performance indexes follow an inverted sigmoid curve whose amplitudes, slopes and inflexion points vary according to the treatment configurations (position and volume of the target). These simulations also showed that the tumor performance indexes are improved thanks to the presence of poorly perfused surrounding tissues, e.g., fat.

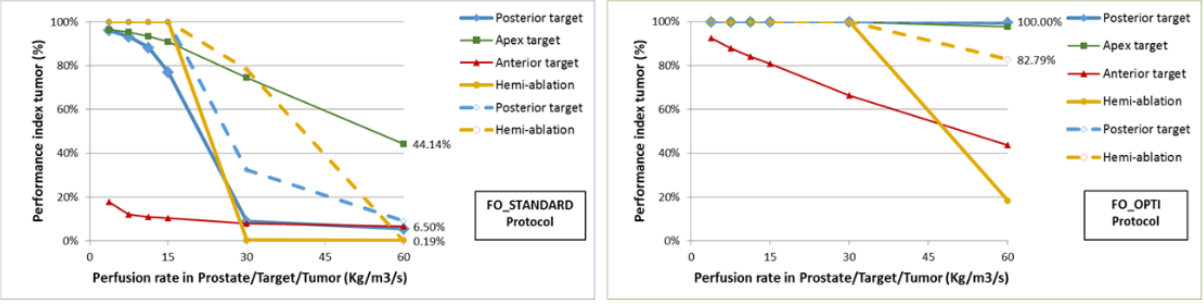

Fig 4: Tumor performance index as a function of the prostate perfusion. Solid lines: perfusion rate of surrounding tissues = 30kg/m^3/s, dashed lines: perfusion rate of surrounding tissues (fat) = 0.5kg/m^3/s.

This study showed that, beyond the blood perfusion, position and volume of the target can influence the focal-treatment rates. Perfusion-dependent sequences would therefore involve complex protocols. Moreover, such sequences could be potentially dangerous for the patient without precise perfusion measurements or if the perfusion varies during treatment. Consequently, it seems to us more judicious to design new less perfusion-dependent sequences (see Task 3.1.2).

RETRO clinical study: intermediate results on the influence of the perfusion

"RETRO" (HIFU/F/18.09) is a data research study according to methodology MR-004 (HCL) which gain approval from the HCL Ethics committee in April 2019. The first bunch of data was collected from a prospective clinical study ("OPTI", HIFU/F/17.12, Eudra CT :2017-A03465-48, inclusions started in March 2018 and ended in March 2020, n=39), which took place between Lyon and Nantes. Patients involved in this study received either focal, half-gland or whole-gland treatment.

We focused our analysis upon the MRI visible tumor to reduce bias and pending the completion of technical developments. The LabTAU first developed a software tool issued from MatLab capable of calculating semi-quantitative perfusion parameters (wash-in, wash-out, time to peak, peak amplitude) within any 3D region attached to the Dynamic Contrast-Enhanced (DCE) sequence. In parallel, EDAP developed a software tool capable of merging the pre-operative and post-operative MRI sequences (HIFUsion MRI-MRI) to compare the planning (typically visible tumor volume increased by its relative margins) to the induced necrosis. More precisely, necrosis to tumor coverage ratio (tumor perfomance index) and others volume-related ratio are computed as well as accuracy indices (DICE, Jacquard).

The intermediate results are presented in Fig. 4.The first observation is that treatment performance (as measured by the necrosis/tumor ratio), is highly variable, and is often surprisingly low. As expected, patients with low perfusion (wash-in<2.7) exhibit high success rates, and most patients with high perfusion (wash-in>7.3) exhibit lower success rates. However, for intermediate perfusion values, the treatment outcome shows high variability and thus cannot be predicted from the perfusion measurement only. Surprisingly, one patient with high perfusion exhibited an excellent treatment performance (~100%).

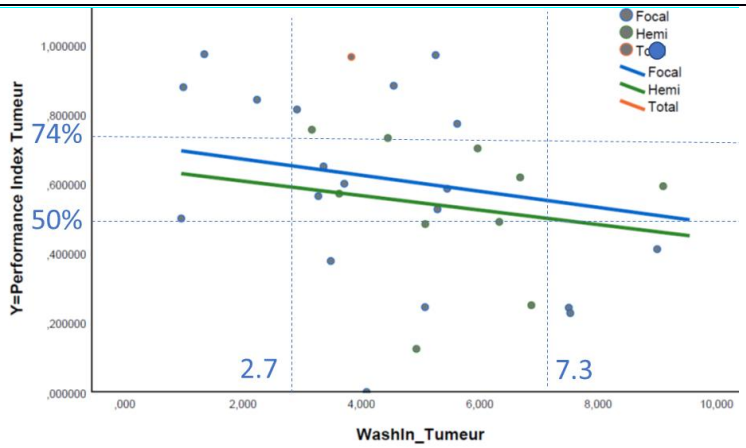

Fig 5: Treatment performance as a function of tumor perfusion (represented by tumor wash-in).

Task 3.1.2: C-Shot F-HIFU sequence

C-shot sequences, based on a more homogeneous spatio-temporal distribution of US energy within the target volume, are the best candidate to improve treatment performances. Depending on the technical constraints of the FocalOne® device, a spatial step of 1 mm between the 40 focal points (from 27 to 67 mm) and a firing duration of 0.2 seconds were chosen. Simulations are currently underway. The aim is to determine an optimal power law (*versus* focusing depth) allowing a target treatment performance close to 100% whatever the treatment configuration and the perfusion rate of the target volume. In order to reduce the processing time, the simulations should also allow determining the optimal movements of the probe (rotation angle and translation step).

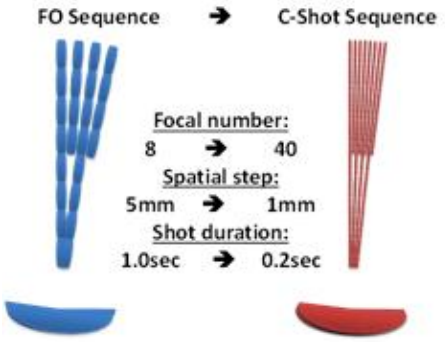

Fig. 6: Comparison between the current FocalOne® sequence and the C-Shot sequence.

The integration of C-shot sequences in the FocalOne® system requires a complete overhaul of the software architecture. A first milestone has been reached with the update of the software element that controls the 16-channel amplifier. The next step is to bring this integration to the software that controls the whole therapeutic process (F1 Therapy). *In vivo* studies are scheduled to start in November 2020 (the protocol authorization request was accepted by the ethics committee).

Task 3.1.4: US Per-operative Perfusion Measurement

In parallel to the C-shot sequence development, we are investigating a technique based on ultrasound thermometry (**Seip et al. 1995**) that was implemented and tested with a Verasonics scanner and a HIFU transducer on a phantom gel (see setup in Fig. 7). A 100 ms duration HIFU shot was performed, then temperature images were acquired every millisecond. The heat spot was not visible in the conventional US images, but it was clearly seen in the temperature images (top right). Finally, simulations were carried out to determine the relationship between perfusion and temperature (bottom right). These results are highly encouraging, demonstrating that it is possible to precisely monitor the temperature rise. Our initial hypothesis was that we would be able to determine perfusion from the temperature measurement, but it turned out that for perfusion rates up to 20 kg/m^3/s, the influence on temperature was negligible (≤ 0.1% relative difference).

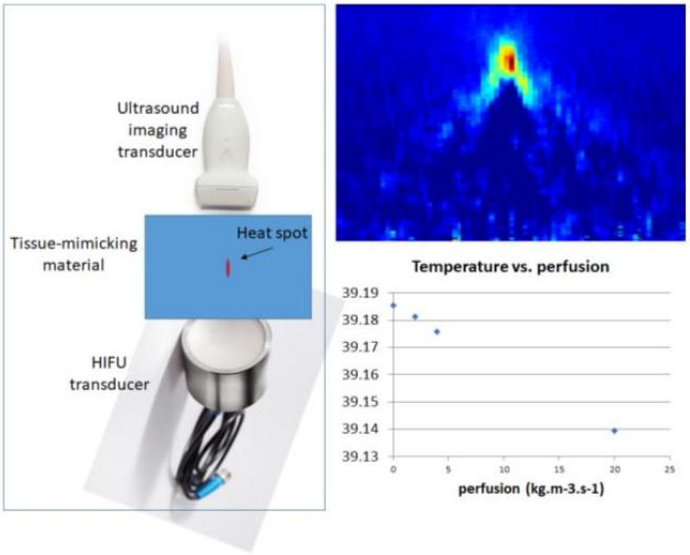

Fig. 7: Scheme of the experimental setup for the per-operative perfusion measurement (left); typical temperature cartography obtained in the phantom gel (top right); temperature values obtained as a result of computer simulations for several perfusion conditions (bottom right).

Even though these findings were unexpected, our US thermometry device allows measuring temperature variation independently of its cause. In the months to come, we will therefore continue investigating the relationship between temperature and treatment outcome, as measured from the coagulation necrosis, in *ex vivo* models.

Task 3.2.1: Design and industrial integration of miniature cMUTs on high density therapeutic HIFU transducers with embedded ultrasound imaging

A new concept of probe based on CMUT technology arose from the specifications defined during the first year of the project. We decided to keep a flat design for both therapeutic and imaging parts, integrating nevertheless a 2D matrix of elements composed of several chips for the therapeutic part.

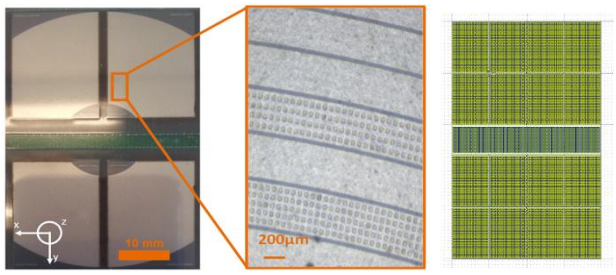

Fig. 8: Left: previous flat design based on 64 rings for the therapeutic part. Right: new design based on a multi-chip assembly composed of a 2D matrix.

This innovative therapeutic design allows for:
- a better production yield via the combination of several smaller chips to build the full probe;
- a scalable design: in the frame of the PERFUSE project, only a limited number of electrical channels will be used by putting several elements in parallel (organized as concentric pseudo-rings).
The main actions were the completion of the acoustic and microelectronic design of the chips for both imaging and therapy.

US imaging

Vermon is in charge of the simulation of the CMUT chips for the imaging part. After analysis of the specification and with the help of Multiphysics numerical tools (which include mechanics, electrical and acoustical domains), more than ten thousand different configurations have been evaluated, which finally resulted in the selection of one dedicated design presenting the following results in transmit and receive modes (Fig.9).

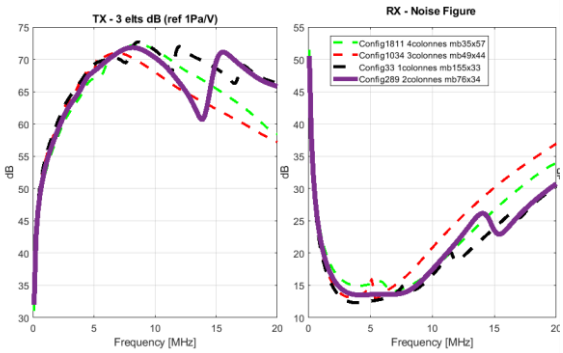

Fig. 9: Simulation results of the imaging part for the transmit (left) and receive (right) modes.

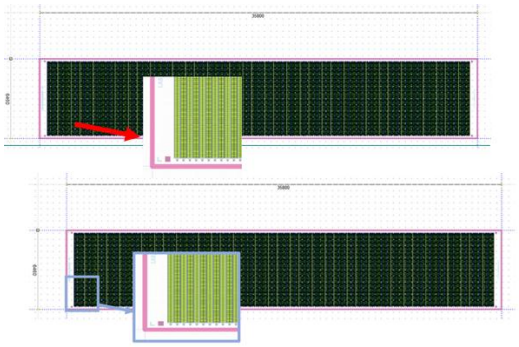

Fig. 10: Layout of the chip dedicated to imaging.

The design of the different photolithographic masks was realized taking into account the simulation output but also the capabilities and the limits of our interconnect and packaging technologies. The imaging probe is composed of 192 elements, with a pitch between elements of 0.19 mm and an elevation of 6 mm, all functioning at a central frequency of 7.5 MHz and designed with the aim of maximizing at the same level the imaging penetration depths and the frequency bandwidth (that is directly linked to the axial resolution). The wafer layout design (Fig.10) is now ready to be manufactured.

HIFU therapy

The LabTAU is in charge of the design of the therapy part. The first objective consisted in defining the best acoustic configuration in terms of element size or number of pseudo-rings for efficient dynamic focusing from a matrix array transducer, while minimizing the number of independent driving electrical channels needed (Reports: 1WAN18-0004, 1WAN18-0005, 4WAN19-0001, 4WAN19-0003, 4WAN20-0001). The pressure field simulation has been managed with the help of the CIVA medical software platform (LabTAU/CEA France) and Fast-ABLASIM, both developed internally by the LabTAU (**Chavrier et al. 2018**).

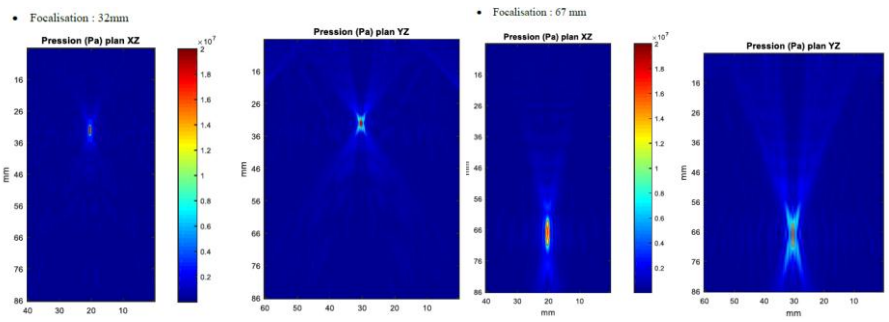

Fig.11: Dynamic focused pressure field at 32 and 67 mm with the new matrix probe design for a pseudo-rings configuration. The obtained results highlight the capability of the new design to treat the prostate at an equivalent distance than the one clinically achieved with the FocalOne®.

Thermal simulations (Fig. 12) were also performed to verify the therapeutic performances of the new 2D matrix design with its pseudo-rings. The achieved results were similar to the ones obtained with FocalOne® piezoelectric probe, and validated thus this configuration for the rest of the project (Report: 4WAN20-0001). It has been defined that a 2D configuration with 6256 mesh elements with a size of 500 µm x 500 µm combined into 64 independent driving electrical channels provides a good trade-off between complexity of design and therapeutic performances. The finalization of the design including geometrical characteristics of CMUT cells and photolithographic mask designs is planned for the second week of July 2020.

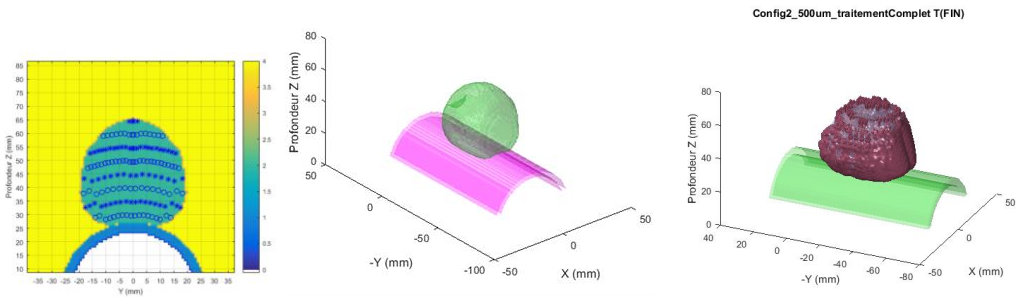

Fig.12: Thermal simulation of HIFU prostate ablation with the 2D matrix probe limited to 64 pseudo-ring.

Task 3.2.2: Preclinical study of high resolution HIFU under US guidance

Experimental study of an earlier version of the US-guided HIFU CMUT probe design (USgHIFU) in preparation for tests on the future PERFUSE prototype

HIFU therapy

Preliminary tests on the first version of a complete prototype of CMUT USgHIFU probe (prior design, "physical rings", MUTATION project) dedicated to prostate application validated the feasibility of generating dynamically focused US for therapy (acoustic fountains). A preliminary qualitative study aimed at generating more intense acoustic fountains than those obtained previously by the LabTAU (**Bawiec et al. 2018**) with the partial prototypes of the MUTATION probe (including only the 64 truncated rings of the therapy part). These acoustic fountains are characteristic of the HIFU power generated (qualitative observation) and of the dynamic focusing (quantitative). For the first time, the rings were power-controlled by bimodal US research US system (Vantage, Verasonics) allowing commands in imaging mode (transient, low power) and in HIFU mode (continuous, high power).

Fig 13: Acoustic fountain generated in HIFU mode with the first prototype of CMUT USgHIFU complete probe for the prostate (previous design in "real ring"). Schematic diagram and result. The acoustic fountain translates the ultrasonic power generation (qualitative) and the good focusing (quantitative: here at f = 52 mm).

However, an intense acoustic fountain (with vaporization phenomenon) could be successfully obtained using the following control parameters: VDC = 90V and VAC = 28Vpp. These results are repeatable over time and observable at several dynamic focal distances (32 to 67 mm). Preliminary tests aimed at quantifying the power generated (acoustic balance measurement) indicate: Iac = 0.2 $W.cm^{-2}$ at the surface of the Tx, at the limit Vac voltage of 28Vpp (only). For now, the limitation to increase power comes from the current limits of the Vantage system (Verasonics).

The LabTAU and Edap are working on a protection system for this research platform which will serve to characterize the future PERFUSE prototype in the laboratory before the power amplifiers planned for the clinic are finalized (Edap).

By focusing dynamically in a thermosensitive gel, a temperature increase of approximately 4°C was obtained on the surface of the phantom and localized in the expected focal volume (measurement with the thermal camera). This result is encouraging but confirms that the electrical controls are still below HIFU requirements. To achieve thermal damage, the temperature increase must be several degrees 10ene in 1s (tissues> 55 ° C.) In order to obtain such a result, it will be necessary to increase the control voltages (VAC and VDC). Also, a medium/long term study of the robustness of CMUTs over time is already underway on this first prototype of a complete probe, in order to guide the tests on future CMUT chips which will constitute the 2nd PERFUSE prototype (new matrix design, pseudo-annular).

US imaging

Higher quality of integrated CMUT linear imaging (resolution) vs. curvilinear imaging integrated into the current clinical system (FocalOne®) has been confirmed on tissue phantoms (Report 1WAN18-0001). These results were used to guide the design and development of an imaging module for the new PERFUSE prototype.

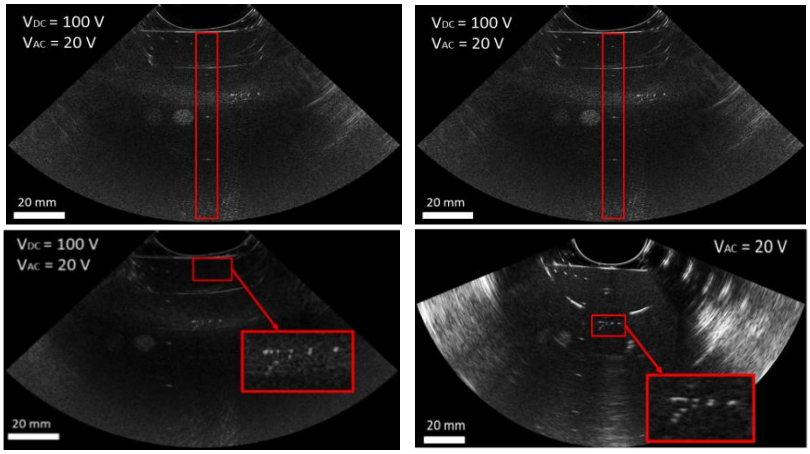

Fig 14: On the top, image acquired with the MUTATION probe (256 CMUTs, plane geometry); on the bottom, images acquired with the FocalOne® probe. Frequency = 7MHz (192 piezoelectric elements, convex geometry). CIRS US phantom.

Task 3.2.3: Industrial integration of the new USgHIFU medical device

Concerning the clinical version of the probe, an important first step has been achieved with the pre-design of the transducer housing (CdC 800908A). It will be redefined after finalization of the CMUT design.

2 ENCOUNTERED DIFFICULTIES

Task 1.1 & 1.2: The inclusion rate for the two clinical trials is lower than expected. Several causes have been identified: stringency of the inclusion criteria, overestimation of the recruitment capacities of some clinical centers, impact of the COVID-19 sanitary crisis and patient's refusal for randomization (HIFUSA). In addition, the administrative constraints (e.g., judicial redress) and the adversarial budgetary strategies further hampered specific centers.
A robust mitigation strategy was therefore implemented, and allowed for: the relaxation of some inclusion criteria; a 12-month-extension of the inclusion period; the involvement of 4 additional centers and the intensification of the follow up (investigator meeting, periodical contacts and newsletters); the presentation of a poster at the AFU annual meeting (Paris) and several dissemination actions (newspaper reports & TV interview of the STR for the program ¨Journal de la Télé, France 5¨).

As the recruitment difficulties persisted, the methodologists and bio-statisticians were asked to provide some updated predictions. They proposed additional mitigation measures which should allow boosting inclusions for both clinical trials: this should allow assessing the results of the FOCALE study before the end of the PERFUSE project despite the cumulated delay, but presumably this will not suffice for the HIFUSA study.
Following these recommendations, the request for a further 12-month-extension of the inclusion period, and for the relaxation of another selection criterion was recently submitted for approval to an Ethic Committee, together with the draft of a flyer aimed at promoting the clinical trials; the inclusion of a Swiss clinical center is almost finalized; a document providing information on the trials was sent to the ¨Union Régionale des Professionnels de Santé¨ in order to encourage general practitioners to directly inform patients. Further communication actions were performed: an interview of the STR was published in the Canceropole Auvergne Rhone Alpes newsletter, HIFUSA and FOCALE trials were promoted within the HCL and the PERFUSE websites, contacts with regional cancer network and patient associations are underway.

Task 1.3: The activation of the PSMA clinical study was delayed due to administrative and security issues: several modifications of the protocol were required by the ¨Association National pour la Sécurité du Médicament¨; the CERMEP laboratory, where the PET/MRI machine is located, did not have the required certification to host a ^{68}*Ga generator.* An alternative solution has been implemented: the ^{68}*Ga-PSMA* radiotracer is produced by the HCL radio-pharmacy and transported to the CERMEP for each exam.

Task 2.1.4: Some difficulties were encountered in hiring a doctoral fellow (>50 applications received, one selected candidate withdrew). The second campaign was initiated during summer 2018 and led to the successful hiring of Audrey Duran. This slightly shifted the scheduled deliverables but will not impair achievement of the global objectives of Task 2.1.3. The ongoing pandemic situation affects the project, but not dramatically. Indeed, significant efforts have been made before the lockdown period to build the image database (including more than 100 patients). Moreover, Audrey Duran mainly performs computer programming; she is currently working from home with access to computing resources and can thus pursue her research activity in correct condition.

Task 2.1.4: Need to redefine the design of the CHANGE study to make sure that the study will be completed by November 2022 (see above).

Task 2.2.2: The current BK Medical EUB-2300 US scanner integrated in the FocalOne® does not provide access to the raw data needed for standard passive elastography. Only B-mode images in which information is already lost beyond recovery are available.

Task 2.2.3: Complex administrative formalities for studies involving healthy volunteers delayed the beginning of the ELASTO-MR clinical trial.

Task 3.1.1: Unreliability of retrospective clinical data delayed the RETRO study.

Task 3.1.3: Due to the high variability of the intermediate results of the RETRO study, the strategy was revolved around the design of sequences which are independent of the perfusion. The multicentric "C-shot" clinical study, therefore, will not be based on 2 arms (low perfused and high perfused patients) but on a single arm of 60 patients with a 1-year follow up. It will start after having completed in-vivo experiments (T3.1.2), at the earliest during the second half of 2021.

Tasks 3.2.1 & 3.2.2: The CMUT manufacturing was delayed due to multiple factors related to the development of a theoretical model for computer simulations of an

unconventional advanced HIFU transducer design (very high density of emitters: more than 10 000 CMUT cells) (~6 months), the definition of the specifications (3 months), several quality control issues at the foundry level (8-12 months), and finally the COVID crisis (3-6 months). Mitigation measures were undertaken: preliminary tests were performed on a prototype of CMUT USgHIFU probe developed for the MUTATION project; the design of a piezoelectric probe to be possibly used in parallel has been chosen.

3 PUBLICATIONS

Computer-aided diagnosis system for characterizing ISUP grade ≥ 2 prostate cancers at multiparametric MRI: A cross-vendor evaluation.
S. Transin, R. Souchon, C. Gonindard-Melodelima, R. de Rozario, P. Walker, M. Funes de la Vega, R. Loffroy, L. Cormier, O. Rouvière.
Diagnostic and Interventional Imaging (2019) 100, 801811
https://doi.org/10.1016/j.diii.2019.06.01

Prostate cancer semantic segmentation by Gleason score group in bi-parametric MRI with self-attention model on the peripheral zone.
Audrey Duran, Pierre-Marc Jodoin, Carole Lartizien.
Accepted for publication in Proceedings of Machine Learning Research 2020
https://openreview.net/forum?id=Ih04Ji3rtN

The research work was detailed in oral and poster presentations at national (SPIMED IA 2019, AFU 2019, EDISS 2019, SFR 2019, JFR 2019, RITS 2019) and international conferences (ISTU 2018 & 2019, IEEE ISU 2018 & 2019, MUT 2019, MIDL 2020).

4 PATENTS

Two invention disclosures are currently being processed. They concern:
- a method for detecting and/or characterizing prostate cancer using magnetic resonance imaging and a computer aided diagnostic system (task 2.1);
- a method for filtering out compression waves in MR elastography (task 2.2.1).

5 SOCIO-ECONOMIC IMPACT PATENTS

Discussions were initiated with the BK Medical System operator to pilot the future designated CMUT imaging probe with a clinical BK US system. A one-by-one non-disclosure agreement was signed for EDAP, Vermon, and is currently being drafted for the LabTAU (via Lyon Ingénierie Projet). The consequence of these preliminary discussions is the lowering of the number of elements from 256 to 192 for direct compatibility with the BK US scanner certified for the clinic.
Several French and international companies were as well contacted regarding the possibility of integrating in the FocalOne® a new US scanner which would provide access to the raw data needed for standard passive elastography.

6 MILESTONES, DELIVERABLES AND SPECIFIC INDICATORS
7 & CONSOLIDATED AGENDA UNTIL THE END OF THE PROJECT

Specific indicators	Status
RHU PERFUSE website	Delivered
Inclusions rate for the prospective clinical trials	Follow up (see A.2)
68Ga PSMA production	Delivered
Prostate cancer targeting with Computer Aided Detection	Ongoing
Integration of passive elastography prototype in the FocalOne®	Ongoing
New probe for imaging and therapy of prostate cancer	Ongoing

Tasks		Milestones - Consolidated agenda		Planned achievement date	Actual achievement date
WP1: Assessment of Focal HIFU Therapy					
1.1	**HIFUSA clinical trial**	D 1.1.1	End of the HIFUSA inclusion period	M12	M46
		D 1.1.2	Evaluation of the adjuvant therapy free rate in both arms	M60	> M60
1.2	**FOCALE clinical trial**	D 1.2.1	End of the FOCALE inclusion period	M24	M46
		D 1.2.2	Evaluation of local control of PCa after F-HIFU	M60	M60
1.3	**PSMA clinical trial**	D 1.3.1	End of the inclusion period : January 2021	M24	M52
		D 1.3.2	Evaluation of the oncological outcome by using a hybrid PSMA-based IRM-PET for FS-HIFU treatment guidance	M60	M60
1.4	**Ancillary clinical trial**	D 1.4.1	Inclusion of FOCALE and PSMA patients	M24	M46
		D 1.4.2	Biological response evaluation	M60	M60
WP2: Diagnosis of prostate cancer foci					
2.1.1	**Collaborative computer-based database**	D 2.1.1 a	Creation of database & importation of existing data	M12	M12
		D 2.1.1 b	Development of data sharing protocol	M18	M18
		D 2.1.1 c	Database with ~300 patients	M36	M23
		D 2.1.1 d	Weekly input of new patients & maintainance	M60	M60
2.1.2	**Quantitative CAD**	D 2.1.2 a	ROI-based QCAD for peripheral zone	M6	M6
		D 2.1.2 b	Image-based QCAD for peripheral zone	M18	M36
		D 2.1.2 c	ROI-based QCAD for transition zone	M30	M30
		D 2.1.2 d	Image-based QCAD for transition zone	M42	M36
		D 2.1.2	QCAD prototype	M42	M42
2.1.3	**Machine Learning- based CAD**	D 2.1.3 a	Benchmark of deep Neural Networks architectures	M18	M24
		D 2.1.3 b	Report on multiclass classification algorithm	M24	M30
		D 2.1.3 c	Deep supervised architecture for peripheral zone	M30	M30
		D 2.1.3 d	Report on domain adaptation method	M36	M42
		D 2.1.3	Machine learning-based CAD prototype	M42	M48
2.1.4	**Multiple center cinical evaluation**	D 2.1.4 a	Results of the DIJON clinical trial	M60	M22
		D 2.1.4 b	Results of the CHANGE clinical trial	M60	M60
2.2.1	**MR elastography**	D 2.2.1 a	MR elastography prototype	M18	M31
		D 2.2.1 b	Report on safety tests	M24	M33
		D 2.2.1 c	Report on performances	M32	M36
2.2.2	**Passive elastography**	D 2.2.2 a	Optimization of elastography for FocalOne probe	M18	M14
		D 2.2.2 b	Prototype evaluation *in-silico* and *ex-vivo*	M22	M22
		D 2.2.2 c	Work on BK images as input of passive elastography	M32	M32
		D 2.2.2 d	Prototype evaluation *in-vivo*	M36	M36
2.2.3	**Clinical evaluation of elastography**	D 2.2.3 a	Report on the ELASTO-MR clinical trial	M60	M60
		D 2.2.3 b	Report on the ELASTO-US clinical trial	M60	M60
WP3: HIFU technical ruptures innovations					
3.1.1	**Perfusion estimation with pre-operative MRI**	D 3.1.1 a	Report on "Retro" study on perfusion	M12	M60
		D 3.1.1 b	Simulations report: perfusion-dependent treatment sequences	M12	M30
3.1.2	**Simulations on C-Shot F-HIFU sequence**	D 3.1.2	Simulations report: "C-shots" treatment sequences	M60	M60
3.1.3	**"C-Shot" dose escalation study**	D 3.1.3 a	Report on pre-clinical "C-Shot" study	M18	M42
		D 3.1.3 b	Report on clinical evaluation of the new HIFU sequences	M60	M60
3.1.4	**US per-operative perfusion measurement**	D 3.1.4 a	Development of US per-operative perfusion measurement technique	M36	M36
		D 3.1.4 b	Design of a new HIFU sequence	M48	M48
		D 3.1.4 c	Evaluation *in-silico, in-phantom* and *ex-vivo*	M54	M54
		D 3.1.4 d	Evaluation of the new HIFU sequences *in-vivo*	M60	M60
3.2.1	**CMUT probe**	D 3.2.1 a	Numerical modelling studies and transducer specifications	M6	M18
		D 3.2.1 b	Micro-electronic design, fabrication and characterization	M15	M33
		D 3.2.1 c	Embedded electronic design	M21	M39
		D 3.2.1 d	Mechanical integration of the device	M30	M48
		D 3.2.1	Report on the design of an industrial cMUT prostate probe	M30	M48
3.2.2	**Preclinical study of HIFU under US**	D 3.2.2 a	Acoustic characterization of USgHIFU prototype	M24	M42
		D 3.2.2 b	*In-vitro/ex-vivo* studies	M30	M48
		D 3.3.2 c	Preclinical *in-vivo* studies	M54	M60
		D 3.2.2	Report on preclinical studies	M54	M60
3.2.3	**USgHIFU medical device**	D 3.2.3 a	Development of a dedicated multi channels amplifier	M24	M48
		D 3.2.3 b	Design of a clinical version of the probe	M48	M57
		D 3.2.3 c	Development of optimal imaging sequences	M24	M40
		D 3.2.3	Prototype of probe usable in clinic for new version of Focal One	M60	M60
WP0: Cooperation and management					
0.1	**Project management**	D 0.1.1	Report of the kick-off meeting and related documents	M1	M1
		D 0.1.2	Report of the steering committees and related documents	Biannually	Biannually
		D 0.1.3	Report of the scientific advisory board and related documents	Annually	Annually
0.2	**Dissemination and communication**	D 0.2.1	Specific RHU PERFUSE website available	M3	M10
		D 0.2.2	Annual and final project reports	M13, M25, M37, M49, M60	M17, M30, M31, M53, M60
		D 0.2.3	External communication materials	M18, M36, M60	M18, M36, M60
0.3	**IP management and transfer**	D 0.3.1	Consortium agreement	M6	M12
		D 0.3.2	Protection of research and development results and other outcomes	Continuously	Continuously

8 SCIENTIFIC MEETINGS OF THE *CONSORTIUM*

Date	Designation	Composition
25/11/2017	Kick-off meeting	PERFUSE partners + ANR
14/2/2018	Steering committee 1	PERFUSE partners
13/6/2018	Steering committee 2	PERFUSE partners
19/9/2018	Steering committee 3	PERFUSE partners
20/12/2018	Scientific Day	PERFUSE partners + ANR + B. Gallix
27/2/2019	SAB meeting	SAB + Leaders WP + project managers
5/3/2019	DRCI meeting: inclusion of foreign clinical investigators	HCL
5/3/2019	Steering committee 4	PERFUSE partners
12/3/2020	Internal meeting: PSMA clinical study protocol	HCL + LABTAU
4/4/2019	Data Safety Monitoring Board	HCL
21/5/2019	Steering Committee 5	PERFUSE partners
5/6/2019	Comex PSMA clinical trial	HCL + LABTAU + CERMEP
13/6/2019	Internal meeting: RETRO clinical study	EDAP + LABTAU
1/10/2019	Steering committee 6	PERFUSE partners
23/11/2020	Meeting with the clinical investigators	HCL + EDAP + Clinical investigators
27/11/2019	Scientific Day & SAB meeting	PERFUSE partners + SAB
25/2/2020	Steering committee 7	PERFUSE partners
13/03/2020	Internal meeting: intellectual property CAD	HCL + CREATIS + LABTAU + LIP
21/4/2020	Internal meeting: CHANGE clinical study	HCL + LABTAU + LIP
15/5/2020	Internal meeting: HIFUSA & FOCALE inclusions	HCL
18/5/2020	Internal meeting: Machine Learning CAD	CREATIS + LIP + LABTAU
26/5/2020	Steering committee 8	PERFUSE partners
5/6/2020 13/6/2020	Internal meeting: industrial collaborations & intellectual property WP3	LABTAU + LIP
Periodical meetings		
Weekly	Coordination meeting	LIP + project manager
Weekly	PERFUSE status report	Scientific coordinator + project manager
Monthly	Steering committee WP3	EDAP + VERMON + LABTAU
Bimonthly	Internal meeting: C-shot sequences	EDAP + VERMON
Bimonthly	Internal meeting: CMUT probe	LABTAU + VERMON

9 CHANGES IN CONSORTIUM MEMBERSHIP

10 FREE COMMENTS

B. SAB Progress Reports

Two meetings with a Scientific Advisory Board composed by Pr. Benoit Gallix, Dr. Stefano Regusci and Mr. Frédéric Sottilini took place in February and November 2019.
Despite several reminders, we only received the report issued from the first meeting.
We enclose, therefore, only this document and encourage the ANR jury members to directly contact Pr. Gallix (Executive Officier of the IHU Strasbourg, benoit.gallix@ihu-strasbourg.eu) to obtain the second report. We apologize for the inconvenience.

	Projet PERFUSE **ANR-17-RHUS-0006** **Rapport SAB n°1**	

Date	**27 février 2019**
Heure	**8h30 - 12h30**
Lieu	Amphi pavillon B - Hôpital Edouard Herriot, 5 Place d'Arsonval, 69003 Lyon
Présent(e)s	**Membres du SAB :** - Pr B. Gallix – Radiologue IHU Strasbourg - Dr S. Regusci – Urologue Clinique Beaulieu Geneve - Mr F. Sottilini – Directeur Général CarThera **Leaders des Workpackages :** - Pr S. Crouzet – RST, Leader WP1 - Pr O. Rouvière – Radiologue - Mr E. Blanc – Directeur R&D EDAP + Cédric Trolliet – Chef de projet LIP (Lyon Ingénierie Projet) Sophie Raquin – Chef de projet RHU PERFUSE

1. Description du projet

Contexte du projet : Les tests de dépistage de l'antigène prostatique spécifique ont augmenté le taux de détection de cancer de la prostate (PCa) qui est maintenant proche de 1 million d'hommes chaque année dans le monde. La prostatectomie radicale demeure un traitement agressif associé à une morbidité importante. Enfin, la stratégie de prise en charge des PCa focaux reste controversée et concurrentielle.

Il n'existe pas encore de traitement conservateur validé disponible pour le PCa. Ainsi, les medecins et leurs patients sont face à deux options extrêmes : la surveillance active, avec le risque de sous-traiter le cancer, d'une part, et les traitements actifs - telle que la prostatectomie radicale ou la radiothérapie- qui sont associés à des morbidités importantes.

Objectifs de PERFUSE :

Le projet PERFUSE a pour objectif d'améliorer et d'évaluer les méthodes de thérapie focale (TF) par HIFU pour le traitement du cancer de la prostate. Ce projet s'intéresse plus particulièrement aux cancers détectés à un stade précoce. Dans un environnement très concurrentiels - de nombreuses thérapies non chirurgicales ont été développées au cours des 20 dernières années - l'approche par HIFU bénéficie d'un avantage de moindre agressivité et pourrait être une méthode prometteuse pour

guérir le cancer sans altérer la qualité de vie tout en évitant une surveillance active anxiogène, onéreuse, et finalement assez complexe quant à la lecture des images d'IRM.

Le projet est décomposé en 4 « workpackages » :

WP1- Son objectif est de réaliser les essais cliniques permettant la validation du traitement focal par HIFU dans « situations distinctes : i) patients à faible risque ii) patients à risque intermédiaire et iii) patients avec une rechute locale après la radiothérapie.

WP2- Ce WP a pour objectif d'optimiser et de standardiser le diagnostic du cancer de la prostate par IRM en utilisant des méthodes d'analyse automatique ou semi-automatique des images afin d'élaborer et de valider un outil d'aide à la décision médicale (CAD)

WP3- le but est d'améliorer l'effet de destruction des HIFU sur les tissus prostatiques en utilisant 2 approches : i) optimiser pour chaque patient la puissance d'énergie qui est délivrée localement en l'ajustant aux paramètres de perfusion évalués par IRM pré-thérapeutique ; ii) développer une nouvelle sonde sur la base d'une technologie non piézoélectrique (cMUT) avec un design de réseau matriciel à forte densité de transducteurs qui permettrait de contrôler spatialement la focalisation et de balayer plus facilement le volume prostatique.

WP0- Structurer et coordonner l'ensemble du projet et veiller à sa bonne exécution

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2. Réunion du jour – présentations :

Le membres du SAB regrettent que des problèmes techniques de visioconférence aient fortement retardé le début de la session de travail et limité les capacités d'échanges et d'interaction avec les porteurs des 3 WPs.
Les présentations faites par les leaders des WP sont de bonne qualité, faite avec transparence et honnêteté.
Une documentation a été fournie avant le meeting ce qui est positif, mais elle reste cependant limitée. Il s'agissait uniquement de la présentation PowerPoint utilisée durant la journée et d'un document de type « Bullet point » d'état des lieux assez succinct. C'est à notre avis insuffisant.

3. Pertinence générale du projet :

Le cancer de la prostate est un problème de santé public mondial et ce projet qui associe des experts académiques du domaine (urologie et radiologie) et des sociétés reconnues pour leur expertise et leur capacité d'innovation peut faire espérer des résultats très innovants. PERFUSE pourraient avoir un véritable impact sur la prise en charge du cancer de la prostate avec un impact bien au-delà de l'hexagone.

PERFUSE propose d'utiliser plusieurs nouveautés technologiques pour la prise en charge diagnostique et thérapeutique du cancer de la prostate dans les WPs 2 et 3s. Le degré d'innovation globale de ce projet n'est pas révolutionnaire, toutes les technologies qui sont décrites (HIFU, IRM, CAD) dans cette proposition existent déjà. L'innovation provient de la coordination de ces outils pour la mise en place d'une prise en charge clinique innovante des patients.

4. Organisation du projet :

Il est regrettable que la construction globale du projet soit inversée avec des essais cliniques (WP1) qui débutent dès le début du projet - utilisant pour cela des technologies commerciales de la société EDAP TMS - alors que les avancées technologiques qui résulteront des WPs 2 et 3 ne pourront pas faire l'objet de tests cliniques en fin de projet. Si l'on comprend aisément que les délais d'inclusion et de surveillance des patients inclus dans les essais cliniques imposaient de commencer très tôt les essais clinique, on peut regretter la multiplication des essais qui complexifient le projet et augmente les risques.

5. Interactions partenaires Industriels et universitaire :

Le PI a une formation scientifique solide et une reconnaissance académique réelle sur le sujet. C'est cependant la première fois qu'il gère en tant que PI un projet de cette envergure (financière, nombre de partenaires, …) et il est donc primordial qu'il puisse dégager - avec l'aide de l'UCBL et des HCL - le temps nécessaires pour que ce projet puisse devenir un succès. D'après le tableau financier le PI est supposé consacrer 50% de son temps à cette recherche !

L'implication du Pr Rouviere pour la partie imagerie est un atout d'une importance capitale. Le PI et le Pr. Rouviere sont des experts mondiaux dans le domaine des HIFU et les HCL ont été à la pointe des évolutions technologiques pour le traitement du cancer de la prostate.

Les partenaires industriels sont des acteurs français solides et anciens des HIFU – société EDAP TMS – ou des transducteurs ultrasonores - société VERMON.
EDAP-TMS, entreprise d'appareils médicaux spécialisée dans la lithotripsie et les ultrasons thérapeutiques a une relation ancienne et privilégiée avec le LabTau et les HCL. Le directeur

technique connaît très bien les ultrasons HIFU. Vermon est excellent dans la production de transducteurs et dispose de ressources ayant l'expertise en technologie cMUT. `

Il semble exister une bonne synergie entre les acteurs académiques et industriels. Cette collaboration étroite et ancienne est favorable au transfert de technologie et à la production de nouvelles connaissances scientifiques.

Les essais cliniques du WP 1 utilisant la technologie commerciale vendue par la société EDAP, il est souhaitable que celle-ci aide s'engage activement dans le succès des essais en proposant le meilleur support commercial et technique auprès des centres recruteurs.

6. Avancement du projet :

Nous retransmettons ici l'avancement du projet par WP tel qu'il nous a été présenté par le PI et les leaders des WPs 2 et 3. Lors du prochain SAB nous souhaiterions aussi pouvoir interviewer individuellement le PI, les leaders des 2 autres WP et la chef de projet.

WP1 : L'objectif est la validation clinique du traitement focal par HIFU dans 3 études différentes pour les patients à faible risque, à risque intermédiaire et ceux présentant une rechute locale après radiothérapie.

L'essai HIFUSA – Étude de phase 3, multicentrique, randomisée, évaluant l'efficacité et la tolérance du traitement HIFU focalisé en comparaison à la surveillance active chez des patients atteints d'un cancer de la prostate significatif de risque évolutif faible. Cet essai est de très loin le plus important. En effet, cette étude est stratégique car elle pourrait permettre, en cas de supériorité du traitement focal, d'ouvrir cette thérapie à une population de patients très importante. C'est donc au niveau de cette étude que les forces doivent se concentrer, d'autant plus que son design multicentrique et randomisé demandera de gros efforts en personnel et ressources matérielles. Actuellement elle n'est ouverte qu'a des centres français avec des difficultés en termes de délais d'ouverture des centres et de recrutement des patients.

Dans la sélection des centres participant à cette étude l'accent devrait être mis sur la qualité des moyens diagnostics, radiologues et IRM ainsi que sur la qualité des biopsies (manipulation des outils de localisation et de fusion US/IRM pour les biopsies). En effet c'est à ce niveau, notamment au niveau de l'interprétation de l'IRM que le succès de la thérapie focale se base en grande partie. Un contrôle de la qualité des IRM, de leur lecture et des biopsies nous semble nécessaire pour chacun des centres ouverts après quelques patients inclus. Un mauvais bilan d'imagerie initial pourrait biaiser les inclusions et rendre l'étude négative.

Avec 6 patients inclus sur 26 théoriques cet essai a déjà pris un important retard. Plusieurs centres ouverts n'ont pas inclus un seul patient. Il existe donc un risque important sur cet essai qui est majeur

pour le projet si l'essai se limite aux centres initialement prévus. **Le SAB recommande l'ouverture de nouveaux centres ayant un fort potentiel de recrutement, si nécessaire à l'international.** Les critères de sélection des patients qui étaient jugés trop restrictifs par certains PI devraient être prochainement élargis avec un amendement.

Étude FOCALE : Étude multicentrique, évaluant le traitement HIFU focalisé chez des patients atteints d'un cancer de la prostate de risque intermédiaire localisé à un seul lobe. Il s'agit d'une étude non randomisée dont l'impact est bien moindre.

Pour les deux études le rôle de la société EDAP est majeur. Elle doit s'impliquer au maximum pour favoriser les inclusions, en simplifiant au maximum tous les problèmes techniques et commerciaux avec les centres.

Étude PMSA : Mono centrique, elle n'a pas encore débuté en raison de difficultés organisationnelles pour la réalisation des PET IRM au PMSA. A suivre…

WP2 :

WP2.1 Mettre au point un système de CAD disponible sur le marché pour améliorer la détection et la localisation du cancer de la prostate sur des images IRM.

Le WP2 bénéficie des travaux de recherche menés par le Pr Rouvière en collaboration avec le laboratoire Creatis. Des bases de donnes d'IRM de prostate conséquentes avec correspondance avec la pathologie étaient déjà constituées avant même le début de PERFUSE et d'autres bases rétrospectives sont progressivement intégrées au projet. Plusieurs thésards ont été recrutés tel que prévu – ou sont en cours de recrutement. Une plateforme d'échange d'IRM anonymisées (S. Gouttard) est en cours de mise en place. Il ne semble pas exister de problème majeur d'agenda sur cette partie du projet.

Point de vigilance : L'objectif est de mettre sur le marché un système de CAD pour la lecture des IRM de la prostate. Malgré cet objectif précis, il ne semble pas y a voir eu d'analyse précise des potentialités de ce WP en matière de création de valeur. **Le SAB recommande de faire faire une évaluation du potentiel de ce travail en termes de propriété intellectuelle et de parcours de certification si besoin est**. Ce travail conditionnera la stratégie en matière de validation sur des BdD rétrospective ou prospective.

Lors de la prochaine présentation il faudra essayer de clairement séparer les parties du projet d'imagerie qui étaient déjà réalisées avant PERFUSE de ce que doit produire PERFUSE.

WP2.2 - Développer de nouvelles méthodes d'élasticité pour l'imagerie de la prostate par IRM

Recrutement d'un thésard au LabTau sur ce sujet. Quelques contraintes techniques à régler telle que la remise en service du setup vibreur elasto qui est en réparation afin de pouvoir débuter les tests sur fantôme. En parallèle début du test des algorithmes de reconstruction.

WP 3

WP3.1 Optimiser pour chaque patient la puissance d'énergie qui est délivrée localement en l'ajustant aux paramètres de perfusion évalués par IRM pré-thérapeutique

La réalisation de cet objectif passe par la réalisation de deux tâches distinctes :

- La première consiste à mieux comprendre le lien qui pourrait exister entre la perfusion des tissus et qualité de la nécrose tissulaire engendrée par les HIFU (WP3.1.1 et WP3.1.4). Pour ce faire, les équipes doivent réaliser une étude rétrospective sur des patients de première intention disposant des données IRM pré et post traitement. Elles ont décidé de façon fort judicieuse d'utiliser les données d'une étude réalisée sur 20 patients à Nantes (OPTI) de manière à disposer de données homogènes venant de patients traités avec les derniers paramètres de l'équipement Focal One d'EDAP TMS. Les mesures de perfusion et les analyses de l'effet de la perfusion sur la qualité de la nécrose seront réalisées par le LabTau durant l'année 2019.
- La seconde consiste à améliorer le dépôt d'énergie, sa précision et son homogénéité en réduisant l'effet de la conduction thermique (WP3.1.2 et 3.1.3). Cela passe par la réalisation de tirs plus courts (200ms vs. 1s avec le Focal One) afin de générer des lésions plus précises. Cette technologie (C-shot) pourrait permettre (d'après les simulations présentées) d'atteindre un niveau de précision jamais atteint et de positionner le traitement HIFU d'EDAP TMS comme LE traitement conservateur du cancer de la prostate. Ces WP sont donc d'une extrême importance pour le succès du traitement proposé. L'intégration de cette technologie C-shot dans le Focal One réclame des développements informatiques et hardwares importants (à réaliser en 2019). **Le SAB recommande donc qu'une timeline solide soit présentée, avec des milestones précis et un suivi détaillé de l'avancement des développements**.

WP3.2 Développer une nouvelle sonde sur la base d'une technologie non piézoélectrique (cMUT) avec un design de réseau matriciel à forte densité de transducteurs qui permettrait de contrôler spatialement la focalisation et de balayer plus facilement le volume prostatique.

EDAP TMS travaille à la réalisation de cet objectif avec la société Vermon, spécialiste du développement et de la production de transducteurs et de sondes OEM pour les fabricants d'échographes. Ces dernières années Vermon a énormément investit dans la recherche et le développement de transducteurs de type C-MUT capables de délivrer la puissance nécessaire aux traitements HIFU. Cette technologie bien que très prometteuse (miniaturisation, intégration avec les circuits électroniques, possibilité de focalisation plus précise, bande de fréquence plus large, vibration plus propre) reste à un stade de développement très précoce. Les simulations présentées lors du SAB1 tendent à montrer que le nouveau design envisagé pour la sonde permettra d'accroitre la précision de la tâche focale. Reste maintenant à confirmer ces résultats par la fabrication. Or, la production de wafer dédiés à la réalisation des sondes à un stade de prototype est longue, coûteuse et présente des risques technologiques importants. Ces risques sont connus et font partie intégrante du projet. Toutefois, **le SAB recommande que soit adoptée dès à présent une stratégie de dérisquage qui permettrait de réutiliser certains éléments de l'électronique de commande qui va être développée pour une utilisation sur une sonde piezo** (nombre d'éléments moins important qu'avec une sonde C-MUT mais plus important que sur le Focal One).

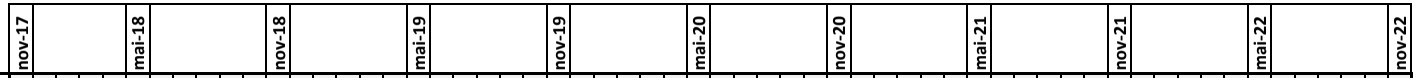
7. Suggestions pour la suite du projet :

Il semblerait utile que l'équipe de coordination, sous la direction du PI, produise un court rapport d'avancement expliquant clairement si les « milestones » ont été atteints ou pas, les raisons éventuelles des retards, les changements ou addendum au projet initial, les risques potentiels ainsi que le résumé des actions de coordinations (nombre de réunion de coordination, résumé des réunions pour chaque WP).
L'investigateur principal semble être débordé par son activité clinique et assez peu disponible pour la coordination du projet. Les membres du SAB rappelle que dans le dossier financier du projet 60 mois de temps de PUPH ont été alloués au projet. Il est donc de la responsabilité de l'UCBL et des HCL de donner les moyens à l'investigateur principal de se libérer pour lui permettre de gérer efficacement de ce projet d'envergure et couteux. Le PI doit en particulier pouvoir jouer un rôle moteur pour le recrutement de nouveaux centres et motiver les centres participant à un maximum d'inclusion.
Le SAB souhaite aussi bénéficier lors de la prochaine journée d'évaluation d'une brève analyse financière du projet avec descriptif analytique simplifié par WP et par partenaire permettant de juger de l'état d'avancement des dépenses pour chaque partenaire.

Gantt chart RHU PERFUSE

Date: 26/6/2020

Achieved
On going
Delayed
Planned

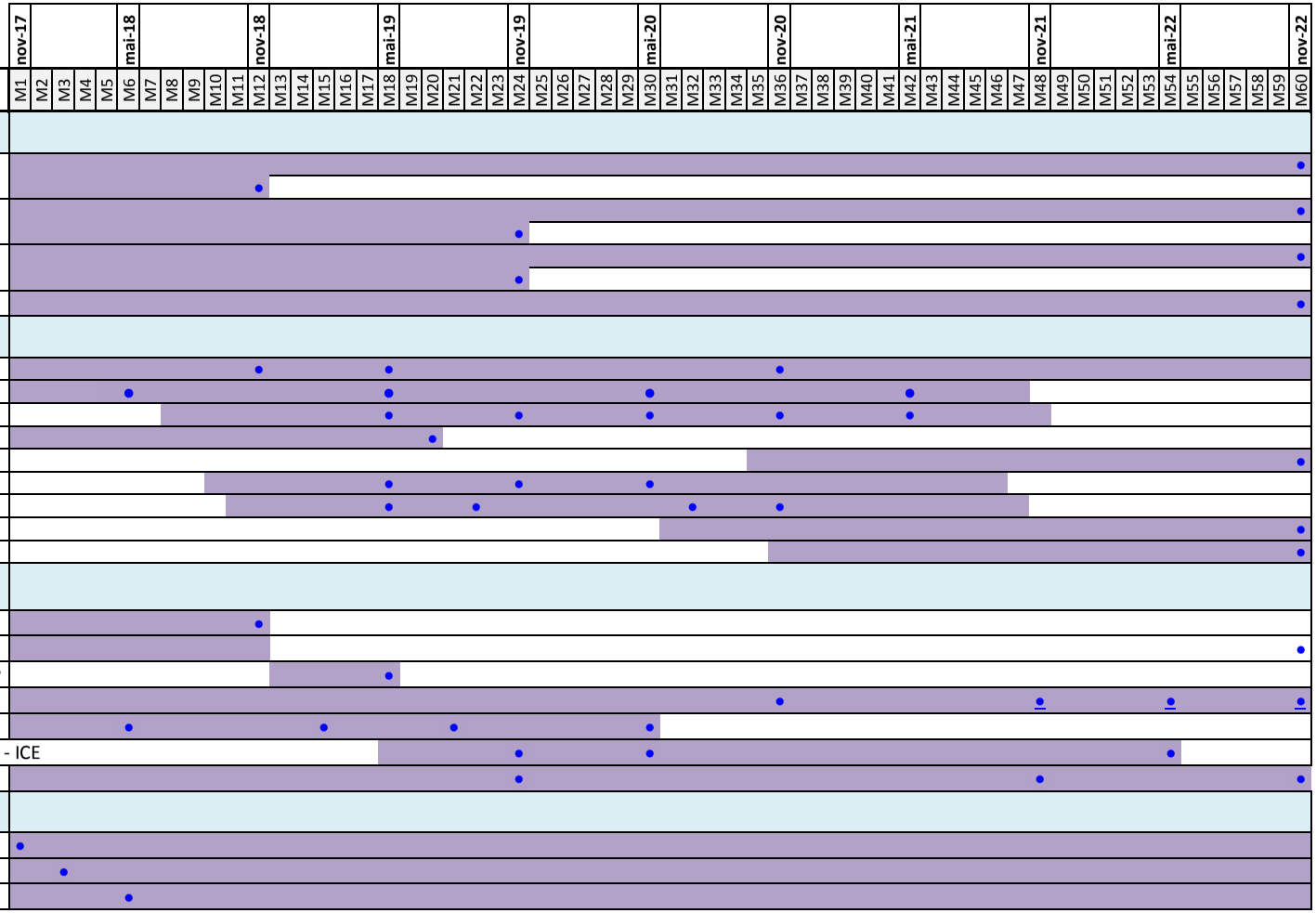


Tasks		Partners
WP1: Assessment of Focal HIFU Therapy		
1.1	HIFUSA clinical trial HiFUSA inclusion period	HCL
1.2	FOCALE clinical trial FOCALE inclusion period	HCL
1.3	PSMA clinical trial PSMA inclusion period	HCL - CERMEP
1.4	Ancillairy clinical trial	CLB - HCL - CERMEP
WP2: Diagnosis of prostate cancer foci		
2.1.1	Collaborative computer-based database	HCL - LABTAU - CREATIS
2.1.2	Quantitative CAD	LABTAU – HCL
2.1.3	Machine Learning-based CAD	CREATIS
2.1.4 a	DIJON clinical trial	HCL
2.1.4 b	CHANGE clinical trial	HCL
2.2.1	MR elastography	LABTAU - HCL
2.2.2	Passive elastography	LABTAU – EDAP
2.2.3 a	ELASTO-MR clinical trial	HCL
2.2.2 b	ELASTO-US clinical trial	HCL
WP3: HIFU technical ruptures innovations		
3.1.1	Perfusion estimation with pre-operative MRI	EDAP + LABTAU
3.1.2	Simulations on C-Shot F-HIFU sequence	LABTAU
3.1.3	C-SHOT dose escalation study	LABTAU - ICE - HCL - EDAP
3.1.4	US per-operative perfusion measurement	LABTAU - ICE
3.2.1	CMUT probe	VERMON - LABTAU - EDAP
3.2.2	Preclinical study of HIFU under US	VERMON - LABTAU - EDAP - ICE
3.2.3	UsgHIFU medical device	VERMON + EDAP
WP0: Cooperation and management		
0.1	Project management	HCL - LABTAU
0.2	Dissemination	HCL - LABTAU
0.3	IP management and transfert	HCL - LABTAU

Preliminary Gantt chart RHU PERFUSE

Date: 26/6/2020

Achieved
On going
Delayed
Planned



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