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BANDO RICERCA SALUTE 2018

PROJECT DATA SHEET

SECTION 1 – GENERAL INFORMATION

Project title

CRyotherapy efficacy Improvement in the treatment of Orthopedic Oncology with Augmented Reality

Project acronym

CRIO2AR

Project coordinator (Principal investigator of the Lead Partner)

Rodolfo Capanna

Term (in months – max 36 months)

36 months

Indicate thematic line (indicate only one line)	☐ *1. Precision Medicine* ☐ *2. Organizational and management research* ☐ *3. Research in oncology:* ☐ *3.1 Biomedical research* *3.2 Translational and clinical research* ☐ *3.3 Epidemiologic research and prevention* ☐ *3.4 Complementary and integrated medicine* ☐ *3.5 Organizational and management research* *x 3.6 Rare tumors*

Project keywords

Clinical therapy trials including surgical intervention, immunotherapy (antibody and cellular), Cryoablation of musculoskeletal tumors Surgical planning, Augmented Reality display

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Abstract *EN/IT* *(max 3000 characters, spaces included)*

Giant cell tumor (GCT) represents 5% of all primitive bone tumors. Standard surgical treatment of GCT includes intralesional excision or segmental resection. The use of local adjuvants such as phenol, alcohol, H_2O_2, Argon or cement as neoadjuvant therapy may decrease recurrence rate, but which local adjuvant works best is still, to this day, controversial. Since tumor cells remain in the new-formed bone, the surgical technique of curettage has to be quite aggressive to avoid higher local recurrence rates. Cryoablation, a local treatment that induces coagulation necrosis, appears to be a good candidate being it more aggressive than standard approaches. Cryoablation has already been used for treating not only for GCT tumors but also for treating benign aggressive bone tumors, both as palliative treatment and as adjuvant therapy but its use as local adjuvant for treating GCT tumors has not been demonstrated as yet.The primary aim of the project is to assess the clinical efficacy of cryoablation as local adjuvant in patient affected by GCT after intralesional surgery vs other adjuvants such as phenol. Clinical efficacy will be assessed in terms of a statistically significant reduction of local recurrence of disease in the first-year follow-up. Secondly, our goal is to compare the clinical outcomes of cryoablation with and without the aid of a dedicated surgical planning platform combined with a wearable Augmented Reality (AR) display. Finally, we shall lay down the specifications of an ideal planning and guidance AR framework that ensures safety and accuracy in cryoablation with the objective to design the most suitable AR visualization modality for guiding each surgical sub-task. To this end, we will develop the AR framework and we will evaluate its efficacy in an in-vitro study on patient-specific replica.

Il tumore a cellule giganti (GCT) rappresenta il 5% di tutti i tumori ossei primitivi. Il trattamento chirurgico standard del GCT include l'escissione intralesionale o la resezione segmentale. L'uso di adiuvanti locali come il fenolo, l'alcol, H_2O_2, Argon o cemento, come terapia neoadiuvante può diminuire il tasso di recidiva, ma quale adiuvante funzioni meglio rimane, a tutt'oggi, controverso. Poiché le cellule tumorali rimangono nell'osso di nuova formazione, la tecnica chirurgica del curettage deve essere piuttosto aggressiva per evitare tassi di recidiva locali più elevati. La crioablazione, un trattamento locale che induce la necrosi coagulativa, sembra essere un buon candidato, essendo più aggressivo degli approcci standard. La crioablazione è già stata utilizzata non solo per il trattamento dei tumori GCT ma anche per il trattamento di vari tumori benigni aggressivi dell'osso sia come trattamento palliativo che come terapia adiuvante, ma il suo uso come coadiuvante locale per il trattamento dei tumori GCT non è stato ancora dimostrato. Lo scopo primario del progetto è di valutare l'efficacia clinica della crioablazione come coadiuvante locale rispetto ad altri coadiuvanti come il fenolo in pazienti affetti da GCT, dopo una chirurgia intralesionale. L'efficacia clinica sarà valutata in termini di riduzione statisticamente significativa della recidiva locale della malattia nel primo anno di follow-up. In secondo luogo, il nostro obiettivo è quello di confrontare i risultati clinici della crioablazione con e senza l'aiuto di una piattaforma dedicata di pianificazione chirurgica combinata con un display in Realtà Aumentata (AR) indossabile. Infine, definiremo le specifiche di un software ideale di pianificazione e guida in AR che garantisca sicurezza e precisione nella crioablazione con l'obiettivo di progettare la modalità di visualizzazione AR più adatta a guidare ogni task chirurgico. A questo scopo, svilupperemo il software di AR e ne valuteremo l'efficacia in uno studio in-vitro su repliche specifiche per paziente.

Total project cost

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431.275 €

SECTION 2 – MASTER DATA (this Section 2 must be filled in Italian)

LISTA DEI SOGGETTI COSTITUENTI IL PARTENARIATO
LIST OF PARTNERS

N°	Responsabile scientifico [1] Scientific Leader [2]	Aziende USL - AOU – enti del SSR – organismi di ricerca Regional Healthcare System organization (AUSL / AOU) – Research Organization	Ruolo (*) Role
1	Rodolfo Capanna	Azienda Ospedaliero Universitaria Pisana. II Clinica Ortopedica Università di Pisa	Coordinatore Scientifico
2	Vincenzo Ferrari	Università di Pisa – Dipartimento di ingegneria dell'informazione	Partner
3			
4			
5			
6			
7			
8			
9			
10			

LISTA DI EVENTUALI SOGGETTI PARTECIPANTI AL PROGETTO – ORGANISMI DI RICERCA NAZIONALI ED INTERNAZIONALI (art. 4 del Bando)
LIST OF PARTICIPANTS
EXTERNAL RESEARCH ORGANISATIONS (art. 4 of the Call)

N°	Denominazione organismo ricerca /Name of Research organization
1	
2	
3	

(*) Nella ricerca possono essere coinvolti soggetti con i seguenti ruoli (art. 3 del Bando):

[1] il responsabile scientifico individuato dal capofila assume il ruolo di Coordinatore Scientifico del progetto

[2] The scientific leader identified by the lead partner assumes the role of Scientific Coordinator of the project

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a) capofila:
b) partner
the research project may involve subjects with the following roles (art. 3 of the Call): a) leader b)partner

FORMA ASSOCIATIVA DEI PARTNERS SCELTA:
ASSOCIATIVE FORM CHOSEN BY PARTNERS:

ATS costituita/constituted
X ATS da costituire/to be constituted
Altro (specificare)/Other (specify)…….

SOGGETTO CAPOFILA/LEAD PARTNER

Ente/Organization	Azienda Ospedaliero Universitaria PIsana
Rappresentante legale **Legal representative**	
Nome e cognome First name and surname	Carlo Rinaldo Tommasini
Ruolo nell'ente Role in the organization	Direttore di Dipartimento
Responsabile scientifico/Coordinatore **Scientific Leader / Coordinator**	
Nome e cognome First name and surname	Capanna Rodolfo
Ruolo nell'ente Role in the organization	Direttore II Clinica Ortopedica Università di Pisa - Azienda Ospedaliero Universitaria Pisana. Professore ordinario in Ortopedia e traumatologia, Università di Pisa
e-mail	rodolfo.capanna@unipi.it
telefono/Phone number	(+39) 050 992025
Curriculum Vitae del responsabile scientifico Curriculum Vitae of the Scientific Leader	See attached CV

PARTNER

Ente/Organization	Università di Pisa – Dipartimento di ingegneria dell'informazione
Rappresentante legale	

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Legal representative	
Nome e cognome First name and surname	Giuseppe Anastasi
Ruolo nell'ente Role in the organization	Director
Responsabile scientifico **Scientific Leader**	
Nome e cognome First name and surname	Vincenzo Ferrari
Ruolo nell'ente Role in the organization	Assistant Professor of Biomedical Engineering
e-mail	vincenzo.ferrari@endocas.unipi.it
telefono/Phone number	(+39) 050 221 7610
Curriculum Vitae del responsabile scientifico Curriculum Vitae of the Scientific Leader	See attached CV

SECTION 3 – PROJECT DESCRIPTION

Idea originating the Project:

Early data support new surgical indications for cryotherapy in the treatment of GCT with relevant results in terms of clinical outcomes {Campanacci, 1990 #12136}. However, no studies have yet evaluated its efficacy versus "standard" surgical approach with conventional local adjuvant (i.e., curettage with phenolic acid as local adjuvant).
In view of this, the principal hypotheses of the project are that:

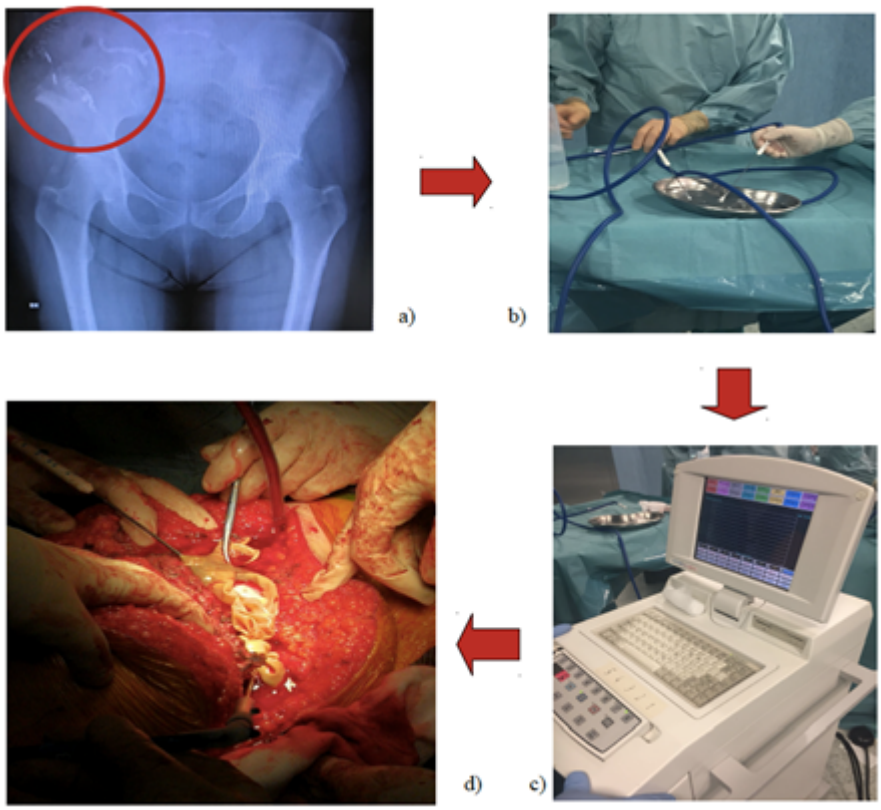
1) Cryotherapy is more effective as local adjuvant in patients affected by Giant Cell Tumor and other benign aggressive tumors than other local adjuvants such as phenolic acid. Our ambition is to demonstrate such statement through a randomized prospective clinical study.
2) In Image-guided surgery (IGS), wearable augmented reality (AR) interfaces based on head-mounted displays (HMDs) are deemed as the most ergonomic solution to aid those medical tasks manually performed under user's direct vision as cryotherapy {Cutolo, 2016 #9056} {Badiali, 2014 #12174} {Cutolo, 2016 #12175} {Cutolo, 2017 #12176}. Our ambition is to demonstrate through an in-vitro study that a preoperative planning framework devoted to cryoablation procedures benefits from the use of patient-specific simulation platforms featuring the use of ergonomic interfaces as commercial AR HMDs.

Here follows a more detailed analysis of the main scientific hypotheses originating our project.
Giant cell tumor (GCT) is a primary intramedullary bone tumor, with a specific predilection for age (i.e., range 20 to 40 years old) and site (i.e., principally distal femur, proximal tibia, distal radio or proximal humerus). GCT is composed of mononuclear and giant mononuclear cells similar to osteoclasts, with a variable and unpredictable growth potential {Campanacci, 1990 #12136}. Surgical treatment options include intralesional excision or segmental resection. Curettage has a higher recurrence rate (20% in tumor with stage 2 or 3 without local adjuvant) but preserve adjacent joint function {Errani, 2010 #12173}. The use of local adjuvants such as phenol, alcohol, H_2O_2, Argon or cement as neoadjuvant therapy may decrease recurrence rate, but which local adjuvant works best is still, to this day, controversial {Errani, 2010 #12172}. The use of adjuvant cryoablation as

local adjuvant for the treatment of GCT has not been demonstrated as yet.
Cryoablation is a local treatment that induces coagulation necrosis by means of rapid freezing, slow thawing, and repetition of the freeze-thaw cycle {Gage, 1998 #12177}. It is based on the Thompson-Joule principle and works by decompressing very rapidly a gas (usually argon) through a needle-like probe. As the argon flows through the needle, a ball of ice crystals forms around the tip of the probe, thus immediately leading to cellular death of the surrounding tissues. Clinically, this therapy has already been used for treating various organ tumors, including those of the kidney {Yamanaka, 2015 #12178}{Rodriguez, 2011 #12179}, liver {Hu, 2014 #12180}, prostate {Bomers, 2013 #12181}, lung {Moore, 2015 #12182}. The hypothesis of this study is that cryotherapy is more effective as local adjuvant in patient affected by GCT after intralesional surgery than other local adjuvants such as poly methyl methacrylate cement or phenolic acid. Cryotherapy is currently used in orthopedic oncology for the treatment of soft-tissue tumors as fibromatosis or angiomas or as an alternative treatment to radio ablation in osteoid osteoma {Schmitz, 2016 #12183} {Wu, 2011 #12184}. Moreover, cryotherapy can be used as adjuvant therapy in open orthopedic surgery to obtain wider surgical margins with possible better results in local control of disease and to control the bleeding thanks to its "solidifying" effect. In some cases, cryotherapy can be used as adjuvant treatment in metastases (MET) or local recurrence (LR) of tumors not conventionally treatable. Cryotherapy was already used in the past as a "poor technique" for its "sterilizing" effect. This technique allows the vital cell component (including tumor cell) to be removed from portions of bone sacrificed during a surgical resection, and therefore it allows the restoring of the otherwise lost bone {Takeuchi, 2015 #12185}. However, only a few studies have been conducted on the efficacy of cryotherapy in percutaneous image-guided cryoablation {Mahnken, 2018 #12186} and, to the best of our knowledge, there appear to be no studies that have evaluated its efficacy in open surgery yet. This project addresses this gap in the literature with a clinical study on image-guided cryoablation in oncologic orthopedic open surgery.
As any surgical procedure, open cryotherapy is more effective, in terms of accuracy and precision if followed by a dedicated and effective preoperative planning. In cryotherapy, such planning framework can be useful for determining the optimal position and orientation of the multiple cryoprobes. A planning software devoted to cryoablation can indeed facilitate the prediction of the synergistic effect of the available cryoprobes on the target bone {Talbot, 2018 #12187}.
In the wider framework of image-guided surgery (IGS), augmented reality (AR) represents a particularly useful asset to improve the surgeon’s spatial perception of the surgical field, because it allows merging the patient specific 3D models generated from preoperative images either contextually to the real patient's anatomy, i.e. as a tool for surgical navigation, or on a physical replica of the anatomy under treatment, i.e. as a tool for surgical simulation/planning {Cutolo, 2016 #9056} {Badiali, 2014 #12174} {Cutolo, 2016 #12175} {Cutolo, 2017 #12176}. Wearable AR systems based on head-mounted displays (HMDs) intrinsically provide the user with an egocentric viewpoint and are deemed as the most ergonomic and easily translatable solution specifically for those procedures, as cryoablation, that are to be performed manually by the surgeon. Therefore, in this project our ambition is to prove that a wearable AR interface can facilitate the smooth and profitable integration of a preoperative planning dedicated to cryoablation into the surgical workflow by improving the interactivity between the surgeon and the planning framework itself.

State of the art and preliminary data:

Clinically, cryotherapy has already been used for treating various organ tumors, including those of the kidney {Yamanaka, 2015 #12178}{Rodriguez, 2011 #12179}, liver {Hu, 2014 #12180}, prostate {Bomers, 2013 #12181}, lung {Moore, 2015 #12182}.



Current surgical application of cryotherapy in open surgery as adjuvant therapy. a) x-ray preop image showing (red circle) a lytic lesion of the right iliac crest from thyroid carcinoma metastases; b) example of the ice ball generated by cryoprobes; c) intraoperative monitoring of the cryoprobes temp. d) "solidifying" effect of cryotherapy and bleeding control of tumor.

Recently, a systematic literature review on the state-of-the-art in percutaneous image-guided cryoablation has been published {Fan, 2016 #12190}. In orthopaedic oncology, cryoablation is established for controlling symptomatic musculoskeletal lesions in palliative cases or as adjuvant

therapy. Cryotherapy proved to be effective in treating benign lesions such as aneurysmatic bone cysts {Tsoumakidou, 2015 #12191} {Griauzde, 2015 #12192}, and in treating locally invasive desmoid tumors with good response rates and tumor progression between 0% and 4 % over 2 years after ablation {Havez, 2014 #12193} {Schmitz, 2016 #12195}. Only few reports regarding malignant primary tumors of the musculoskeletal system are available {Fan, 2016 #12190}. Fan et al. reported a significant pain reduction from 7.49/10 to 5.44/10 (p = 0.01) on a visual analog scale after cryotherapy of cases of retroperitoneal sarcoma relapse {Fan, 2016 #12189}. The treatment of musculoskeletal metastases in oligometastatic patients has also been evaluated in large retrospective series with variable local tumor control: 67 % in bone lesions and 97% in soft tissue lesions after 21 months {McMenomy, 2013 #12188}. Finally, in orthopaedic open surgery cryoablation proved its efficacy as method for recycling tumor-bearing autografts without cryoprobe (i.e.,"poor technique") but immersing the autograft in liquid nitrogen for "sterilizing" it by cells of tumor or as adjuvant to expand surgical margins (i.e.,"probe technique") under fluoroscopic assistance.

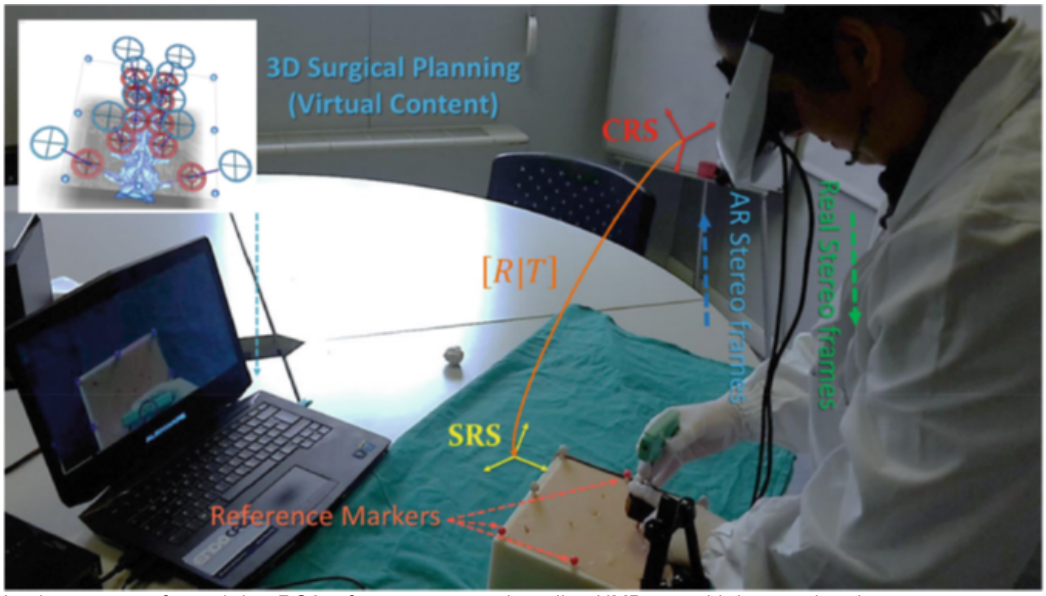
In 2010 Errani C et All. {Errani, 2010 #12172} present a review of 349 cases of GCT of extremity treated from a single institution. The hypothesis of this study was that an "aggressive curettage" with phenol, alcohol and cement provides better local control and functional results.

Recently Dabak N et All, described advantages of Pressurized-Spray Cryosurgery in Giant Cell Tumors of the Bone {Dabak, 2016 #12236}. The study included 40 patients who were treated with extensive curettage and cryotherapy at various locations during the period from February 2006 to December 2013. Authors concluded that cryotherapy was highly effective in treating the lesions, especially those located in the femur and tibia and remained insufficient in the lesions expanded outside the cortex. Wound healing problems, infection and fracture risk proved to be lower with this technique.

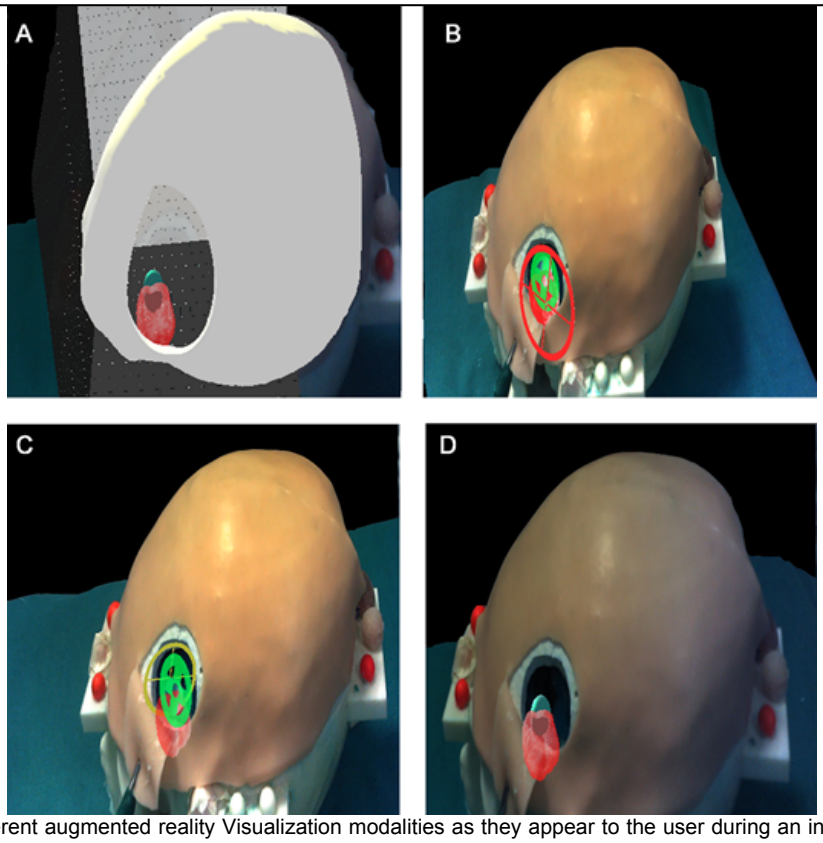
Recently, we published a retrospective study involving 143 patients in which cryotherapy proved its efficacy in further increasing local control of disease with respect to standard treatment without cryotherapy {Colangeli S, 2019}.

The emerging of modern medical imaging technologies has represented a revolution in medicine, targeted at the diagnosis as well as at the therapy. Image-guided surgery (IGS), for diagnostic and therapeutic purposes, is carried out by coupling clinical data with information deriving from the elaboration of medical images. Medical images can be loaded into software platforms for surgical planning and medical/surgical navigators to improve diagnosis and therapy as follows: by providing a three-dimensional visualization of the anatomy and of the pathology, by improving accuracy and efficacy of the treatment procedures {Picardo, 2012 #12241}, by reducing their invasiveness, and by aiding the precise execution of the intervention as dictated by the preoperative planning. Current limits of IGS systems are mainly due to the increase of the surgical time needed for system setup and management and to the increase of technical complexity in the surgical workflow. In the realm of IGS systems, augmented reality (AR) technology has appeared to represent a significant development, because it was regarded as capable of providing the surgeon with the ability to interact with the radiological images and surgical planning contextually to the real patient anatomy {Kersten-Oertel, 2013 #12244}. AR visualization modalities can in fact provide the surgeon with a direct perception of where the virtual content is located within the surgical field, by merging the patient specific 3D models either contextually to the real patient's anatomy, i.e. as a tool for surgical navigation, or on a physical replica of the anatomy under treatment, i.e. as a tool for surgical simulation/planning {Ferrari*, 2009 #12245}. Those visualization modalities have been designed to act either as surgical guidance or as tools for surgical planning or for diagnosis {Peters, 2000 #12246} {Peters, 2006 #12247}. Thereby, the idea of integrating the surgeon’s perceptive efficiency with the aid of new AR visualization modalities has become a dominant topic of academic and industrial research in the medical domain since the 90’s. In the last years, AR-based IGS systems for maxillofacial surgery,orthopedic surgery, and neurosurgery have been increasingly tested, even if mostly at research level. Wearable AR systems based on HMDs intrinsically provide the user with an egocentric viewpoint, and by generating both binocular parallax and motion parallax, they smoothly

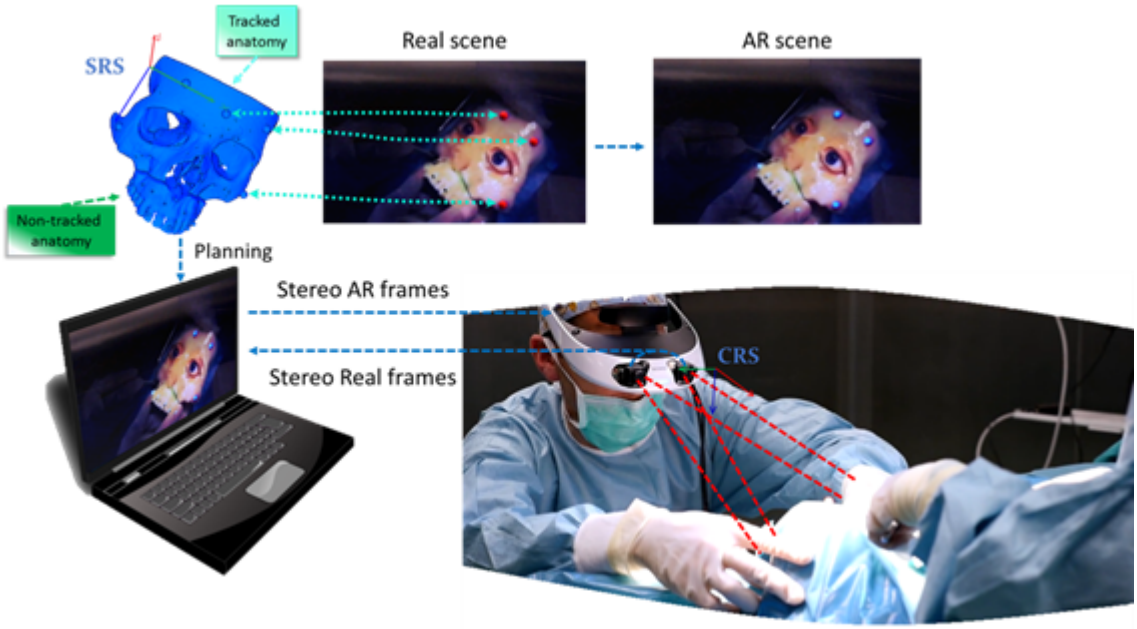
augment the user's perception of the surgical scene.
The Department of Information Engineering of the University of Pisa (RO2) through the EndoCAS Center for Computer Assisted Surgery has an in-depth experience in the design, development and validation of surgical navigation systems and surgical simulators with AR interfaces {Cutolo, 2017 #9208} {Cutolo, 2016 #7711} {Cutolo, 2015 #11274} {Cutolo, 2016 #11092}{Ferrari, 2015 #7647} {Badiali, 2014 #11207 }{Cutolo, 2014 #11200}{Carbone, 2018 #11567}{Turini, 2018 #11568}{Viglialoro, 2016 #7593}{Condino, 2016 #12056}{Condino, 2018 #12132} {Ferrari, 2015 #7480}. RO2 has proved in vitro the efficacy of wearable AR platforms as surgical navigation systems to aid several manual procedures. Studies were conducted in maxillofacial surgery for allowing maxillary repositioning, in neurosurgery for aiding complex neurological lesion targeting {Badiali, 2014 #12174}, and in orthopedic surgery for aiding closed reduction of long-bone fractures and for assisting vertebroplasty percutaneous procedures {Cutolo, 2016 #9211} {Cutolo, 2016 #12045}.



In-vitro test performed by RO2 of an augmented reality HMD as aid in vertebroplasty percutaneous procedures. The software application merges the 3D surgical planning (virtual content) with the stereoscopic views of the surgical scene (real stereo frames) grabbed by the stereo rig. The AR stereo frames are sent to the two internal displays of the visor. Alignment between real and virtual information is obtained through a marker-based tracking algorithm {Cutolo, 2016 #7711}.



Four different augmented reality Visualization modalities as they appear to the user during an in vitro test on neurosurgery. The AR information is intended to aid the surgeon during neurological lesion targeting tasks: A) 3D grid effect, B) Occluding virtual viewfinders, C) Non-occluding virtual viewfinders, D) Anatomical Occlusions and transparencies. {Cutolo, 2017 #9208}



Video see-through paradigm of the stereoscopic HMD used to aid maxillary repositioning. {Cutolo, 2015 #11274}

Further, RO2 has an extensive experience in the development of patient-specific replica of

anatomical structures for orthopedic surgical planning {Parchi, 2013 #11470} {Parchi, 2016 #12252} and surgical/medical training {Condino, 2011 #7162} {Condino, 2018 #12132} {Carbone, 2011 #5699} {Pacioni, 2014 #7116}, which is key also for the implementation of AR-based or VR-based simulators for training in surgery and interventional radiology {Viglialoro, 2014 #7358}{Turini, 2017 #8971} {Parrini, 2014 #9234}. The consortium has a comprovated experience in the development of orthopedic surgical simulators and in the organization of course for surgeon education in total hip arthroplasty using 3D real model of the patient's anatomy and a standard surgical instrumentation {Parchi, 2016 #12252} {Parchi, 2016 #7479}.

(a) (b) (c)

Examples of AR images of an Hybrid Simulator developed by RO2 captured during the simulated surgical procedure: (a) the mannequin, positioned on a surgical table and covered with a surgical drape to enhance the realism of simulation, and the virtual AR menu for the selection of the virtual anatomical components to be visualized; (b) the surgeon can visualize in AR mode the virtual anatomy before performing the surgical incision; (c) with the help of the virtual viewfinder, the surgeon can orient the surgical instrument, so that the acetabulum reaming can proceed in the direction of the planned implant {Condino, 2018 #12132}.

General goal of the Project and related strategy / experimental design:

Operational Objectives:

Below a list of Operational Objective with indication of the responsible partner

Operational Objective 1 (OO1): Project Management & Dissemination (RO1)

Activity 1.1 Administrative coordination

Activity 1.2 Scientific coordination

Activity 1.3 Dissemination

Operational Objective 2 (OO2): Clinical Test (RO1)

Activity 2.1 Design of the clinical protocol

Activity 2.2 Documentation for Ethics committee approval

Activity 2.3 Clinical trial

Activity 2.4 Clinical data collection

Operational Objective 3 (OO3): Demonstrator of an AR platform for planning & guidance (RO2)

Activity 3.1 Specification for AR planning & guidance

Activity 3.2 Specification for in-vitro set-up

Activity 3.3 Development of the AR software framework for planning and guidance

Activity 3.4 Implementation of the physical simulators for in-vitro test

Activity 3.5 In-vitro test

Activity 3.6 In-vitro data collection

Operational Objective 4 (OO4): Data Analysis (RO2)

Activity 4.1 Analysis of clinical data

Activity 4.2 Analysis of in-vitro tests

Operational Objective no. (1)

Name: PROJECT MANAGEMENT (RO1)

Description of the operational objective:

- Implementation of all the management activities, including on-time payment of the funds

allocated to all consortium partners and the corresponding reports to the region;
- Monitoring and Coordination of the research activities and their congruence with the project Gantt;
- Organization of the project meetings, including preparation of the meetings' minutes;
- Monitoring of the Milestone achievement and Deliverable preparation;
- Maintaining contact and carry out all fulfilment required by the Tuscany Region;
- Risk management: including clinical risks (related to the clinical trial), technological risk and financial risk which can limit the future adoption of the proposed AR approach;
- Monitoring of financial and resource planning of the overall action, including ensuring on-time preparation and release of project periodic/final financial reports;
- Monitoring of compliant use and administration of the funding;
- Coordination actions to ensure smooth communication between partners and with the region and its representatives;
- Identification of the possibility to protect the technological solutions designed in the project with the submission of a patent.
- Dissemination of the project results through the creation of a public website dedicated to the project; the publication of scientific papers in national and international journals; the participation to national and international conferences.

Expected Results: deliverables e milestones

DELIVERABLES:
- D 1.1: Intermediate technical report and intermediate financial report (18th month - Task 1.1 & Task 1.2)
- D 1.2: Final technical report and financial report (36th month - Task 1.1 & Task 1.2)

MILESTONES:
- M 1.1: Verification of work progress and intermediate financial report (18th month - Task 1.1 & Task 1.2)
- M 1.2: Verification of project completion and final financial report (36th month - Task 1.1 & Task 1.2)

Timing: 36 months (1:36)
Total cost of the objective: *49862,06 €*
List of activities envisaged under the Operational Objective:
Activity no. 1.1 Administrative coordination - Cost: 14291,9 €

Activity no. 1.2 Scientific coordination - Cost: 14291,9 €

Activity no. 1.3 Dissemination - Cost: 21275,26 €

Activity no. 1.1 - Name: Administrative coordination

- Implementation of all the management activities, including on-time payment of the funds allocated to all consortium partners and the corresponding reports to the region;
- Maintaining contact and carry out all fulfilment required by the Tuscany Region;
- Monitoring of financial and resource planning of the overall action, including ensuring on-time preparation and release of periodic and final financial reports;
- Monitoring of compliant use and administration of the funding;

Tools/equipment: PC (already available)

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

Staff (full time person month)

AUOP: Orthopedic Surgeon/Professor: 0.2 p.m (docente medico AUOP) , Orthopedic Surgeon (dirigente medico): 0.23 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Assegnista 1.41 p.m
UNIPI: Senior PhD Engineer 1.2 p.m

Total Personnel (full time person month) 3,04

Subcontracts:
No need for subcontracts

Expected results: Deliverables and/or Milestones
Deliverable D 1.1: Intermediate technical report and intermediate financial report (18th month)
Deliverable D 1.2: Final technical report and financial report (36th month)
Milestone 1.1: Verification of work progress and intermediate financial report (18th month)
Milestone M 1.2: Verification of project completion and final financial report (36th month)

Timing: 36 months From project beginning to the end - Month 1: Month 36

Activity no. 1.2 - Name: Scientific coordination
The coordinating institution will monitor and evaluate the activity of the project, to ensure the achievement of the goals of the project. The scientific coordination will include the:

- monitoring and coordination of the research activities and their congruence with the project Gantt ;
- organization of the project meetings, review meetings, including preparation of the meetings' minutes;
- monitoring of the Milestone achievement and Deliverable preparation;
- maintenance of contacts with Tuscany Region to carry out all the required fulfilments;
- risk management: including clinical risks (related to the clinical trial), technological risk and financial risk which can limit the future adoption of the proposed AR approach;
- coordination actions to ensure smooth communication between partners and with the region and its representatives;
- identification of the possibility to protect the technological solutions designed in the project

with the submission of a patent.

Tools/equipment:
PC (already available)

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

Staff (full time person month)

AUOP: Professor: 0.2 p.m (docente medico AUOP) , Dirigente medico 0.23 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Assegnista 1.41 p.m
Senior PhD Engineer 1.2 p.m

Total Personnel (full time person month) 3,04

Subcontracts: No need for subcontracts
Expected results: Deliverables and/or Milestones
Deliverable D 1.1: Intermediate technical report and intermediate financial report (18th month)
Deliverable D 1.2: Final technical report and financial report (36th month)
Milestone 1.1: Verification of work progress and intermediate financial report (18th month)
Milestone M 1.2: Verification of project completion and final financial report (36th month)

Timing: From project beginning to the end - Month 1: Month 36

Activity no. 1.3 - Name: Dissemination

Creating a sound dissemination strategy for the research project will lead to increased awareness of the research and, therefore, maximize the impact that the research can have in improving the health outcomes of the patients that will benefit from it.
The dissemination actions will include:

- the creation and the periodic update of a public website dedicated to the project;
- the publication of scientific papers in leading-edge medical and technical peer reviewed Journals (including Open Access journals) such as: Orthopedic Oncology; Journal of Orthopedics research; Clinical Orthopaedics and Related Research transaction on Biomedical Engineering; Computer Assisted Surgery:
- the participation to national and international, medical and technical conferences such as: Emsos (annual Meeting of the European Musculoskeletal Oncology Society), The International Conference on Orthopedic Surgery, Caos International (international society for computer assisted orthopaedic surgery), EuroVR.

Tools/equipment: PC (already available)

Human resources:

Staff (full time person month)

AUOP: Professor: 0.1 p.m (docente medico AUOP) , Dirigente medico 0.4 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Assegnista 1.18 p.m
UNIPI: Engineer PhD Student 1.2 p.m; Senior PhD Engineer 0.48 p.m

Total Personnel (full time person month) 3,36

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

Timing: 36 months (1:36)

From project beginning to the end - Month 1: Month 36

Operational Objective no. (2)

Name: CLINICAL TEST (RO1)

Description of the operational objective:

This operational objective will be devoted to the design and execution of a prospective, randomized, controlled, three arms clinical trial for the treatment of giant cell tumors comparing: traditional surgical approach with conventional preoperative planning, cryotherapy approach with conventional preoperative planning, and cryotherapy approach with augmented reality preoperative planning.
This OO includes: the design of the clinical trial, the preparation of all the documentation of the Ethics committee approval, a careful clinical data collection during the execution the clinical trial. Collected data will be analyzed in OO3.

Expected Results: deliverables e milestones

DELIVERABLES

- D2.1 Report on clinical protocol with the surgical planning application (Task 2.1 - 5 month)
- D2.2 First 10 Patient Reports: first impressions, feedbacks and adverse events reports (Task 2.3 - 14 month)
- D2.3 Final Medical reports, comments, feedbacks and adverse events reports (Task 2.3 - 24

month)
- D2.4 Final reporting on collected data (Task 2.4 - 36 month)

MILESTONES

- M2.1 Submission of the clinical protocol to the hospital ethical committee (Task 2.2 - 6 month)
- M2.2 Clinical protocol approval by the hospital ethical committee (Task 2.2 - 8 month)
- M2.3 First 10 patient treated (Task 2.3 - 14 month)
- M2.4 Conclusion of the patient recruitment phase (Task 2.3 - 24 months)
- M2.5 Data collection concluded (Task 2.4 - 36 month)

Timing:
30 months (1:30)

Total cost of the objective:
103613,54 €

List of activities envisaged under the Operational Objective:
Activity no. 2.1 - Name: Design of the clinical protocol - Cost: 6698,52 €

Activity no. 2.2 - Name: Documentation for Ethics committee approval - Cost. 7997,25 €

Activity no. 2.3 - Name: Clinical trial - Cost: 71274,49 €

Activity no. 2.4 - Name: Follow-up and Clinical data collection - Cost: 17643,28 €

Activity no. 2.1 - Name: Design of the clinical protocol

All the patients with the diagnosis of giant cell tumors admitted to department of the P.I., for which there will be the indication for an open surgery treatment of benign aggressive bone tumors, will be randomized to one of two protocol of treatments under study: a standard procedure [tumor curettage or resection, augmentation with poly methyl methacrylate cement and phenolic acid as adjuvant therapy] [Control Group] or a standard procedure + cryotherapy treatment [tumor curettage or resection, cryotherapy as adjuvant therapy] [CRYO group]. The patients included in the CRYO group will be randomized themselves to receive either a conventional preoperative planning [CRYO-X group] or a preoperative planning based on real procedure simulation with an augmented reality visor [CRYO-AR group].
The principal endpoint for the effectiveness of the procedure will be: the presence of local recurrence of disease in the first year follow-up.
Moreover, the effectiveness will be also measured in terms of duration of the total surgical intervention.
The secondary outcome measures will be also:
- QALY (Quality Adjusted Life Year). At this aim the EQ5D-5L questionnaires will be administered to patients.
- Quality of work. Ad hoc questionnaires will be designed and administered to the hospital personnel for assessing differences in quality of work related to the adoption of the cryotherapy treatment and the AR preoperative planning.

The secondary clinical endpoints will be identified to allow a multidimensional comparison of the proposed approach; a first list is reported below:
- intraoperative Blood Loss;
- radiation exposure;
- complication rates;

- postoperative infections.

Tools/equipment: *PC*

Human resources:
Staff (full time person month)
AUOP: Expert Orthopaedic Surgeon/Professor: 0.05 p.m, Orthopaedic Surgeon 0.1 p.m
R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)
AUOP: Orthopaedic Resident Surgeon 2.1 p.m
Total Personnel (full time person month) 2,25

Subcontracts: *No need for subcontracts*

Expected results: Deliverables and/or Milestones

DELIVERABLES
D2.1 Report on clinical protocol with the surgical planning application (Task 2.1 - 5 month)

Timing: 5 months (1:5)

Activity no. 2.2 - Name: Documentation for Ethics committee approval

This task will be devoted to the preparation of the documentation for the ethics committee including:
- Patient Information Sheet;
- Patient Consent form;
- Information form for the treating physician;
- Description of the study protocol;
- Data collection form;
- Letter of intent;
- Letter for requesting opinion to the AUOP Healthcare Director and Ethical committee.

Tools/equipment
- operating room with all the equipment for orthopedic surgery
- cryotherapy equipment will be ensured through specific agreement with private provider

Human resources:

Staff (full time person month)

AUOP: Expert Orthopaedic Surgeon/Professor: 0.05 p.m, Orthopaedic Surgeon 0.1 p.m
UNIPI: Engineer Senior Researcher: 0.84 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Orthopaedic Resident Surgeon 1.05 p.m
UNIPI: Senior PhD Biomedical Engineer 0.24 p.m

Total Personnel (full time person month) 2,28

Subcontracts: *No need for subcontracts*

Expected results: Deliverables and/or Milestones

MILESTONES
M2.1 Submission of the clinical protocol to the hospital ethical committee (Task 2.2 - 6 month)
M2.2 Clinical protocol approval by the hospital ethical committee (Task 2.2 - 8 month)

Timing: 4 months (5:8)

Activity no. 2.3 - Name: Clinical Trial

All the patients enrolled in the study, as usually, will be preoperatively evaluated with tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) or bone scintigraphy for the diagnosis and the staging of the lesion. The diagnosis will be confirmed by an histologic analysis. After the recruitment phase, all the Patients will be randomized as described in task 1.1. For the Control Group the preoperative planning will made from the P.I. on the basis of the preoperative data; for the CRYO-X group the preoperative planning, including the cryoprobes disposition, will made from the P.I. on the basis of the preoperative data; for the CRYO-AR group the preoperative planning, including the cryoprobes disposition, will be made using:

- a real procedure simulation based on a 3D replica of the tumor and of the main anatomical structures nearby the mass (nerves, vessels, spinal cord, organs ...)
- a commercial augmented reality head-mounted display (Microsoft Hololens) provided by the technical partner of the project that allow aiding the cryoprobes insertion on in-vitro patient-specific mannequins. During the in-vitro simulated procedure the criprobes insertion will be guided with the AR system, based on a virtual preoperative planning, in order to optimize their insertion to treat the maximum part of the tumoral mass without damage the surrounding anatomical structures. After cryoprobes insertion, the data of each probe (area of insertion, angle of insertion, deep of insertion) in relation to easily identifiable anatomical structures will be recorded. The day of the surgical procedure the surgeon will be aid in the cryoprobe insertion with the direct visualization of the 3D model (with the probes inserted) and with data recorded (area of insertion, angle of insertion, deep of insertion) during the in vitro test.

Tools/equipment:
- operating room with all the equipment for orthopedic surgery
- cryotherapy equipment will be ensured through specific agreement with private provider
commercial AR HMD (Microsoft Hololens)
- a workstation/laptop dedicated to the planning software

Human resources:
Staff (full time person month)
AUOP: Expert Orthopaedic Surgeon/Professor: 0.4 p.m, Orthopaedic Surgeon 1.22 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)
AUOP: 2 Orthopaedic Resident Surgeons for a total of 13.43 p.m
Total Personnel (full time person month) : 15,05 p.m

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones
DELIVERABLES
- D2.2 First 10 Patient Reports: first impressions, feedbacks and adverse events reports (Task 2.3 - 14 month)
- D2.3 Final Medical reports, comments, feedbacks and adverse events reports (Task 2.3 - 24 month)

MILESTONES
- M2.3 First 10 patient treated (Task 2.3 - 14 month)
- M2.4 Conclusion of the patient recruitment phase (Task 2.3 - 24 months)

Timing: 16 months (9:24)

Activity no. 2.4 - Name: Follow-up and Clinical Data Collection

During the surgical procedure, in all the three groups [Control, CRYO-X, CRYO-AR], data will be collected regarding: intraoperative blood loss, length of surgery, X-ray exposition and any complications related to the procedure.
Data from the medical records regarding pain control (NRS score), postoperative bleeding (Hb levels, blood transfusions), length of hospitalization and any complications will be recorded.

All the patients will be clinically evaluated at 1, 2, 6, 12, months after the surgical procedure. A EORTC QLQ-C30 questionnaires will be given to patients pre and post operatively at 2, 6, 12 months to objectively measure the clinical outcomes in all groups. Follow-up CT-scans or MRI control, as usual, will be made at 2, 6 and 12 months from the procedure for detecting postoperative local recurrence or disease progression. Any complications occurred during the follow-up period will be recorded.
An ad-hoc questionnaires will be designed and given to the surgeons for assessing differences in quality of work related to the adoption of the dedicated AR system for planning [CRYO-AR] compared to the standard planning [CRYO-X group]. All these post-operative examinations are already included in standard monitoring protocol of oncological guidelines.

Tools/equipment:
- operating room with all the equipment for orthopedic surgery
- cryotherapy equipment will be ensured through specific agreement with private provider

Staff (full time person month)

UNIPI: Engineer Senior Researcher: 0.27 pm

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Orthopaedic Resident Surgeon 5.43 p.m
UNIPI: Senior Engineer PhD 0.24 p.m

Total Personnel (full time person month) 5,94

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones
DELIVERABLES
- D2.4 Final reporting on collected data (Task 2.4 - 36 month)

MILESTONES
- M2.5 Data collection concluded (Task 2.4 - 36 month)

Timing: 28 months (9:36)

Operational Objective 3 (OO3)

Name: DEMONSTRATOR OF AN AR PLATFORM FOR PLANNING AND GUIDANCE (RO2)

Description of the operational objective:

This operational objective is devoted to the development and testing of an AR platform for planning and guidance of the target intervention. Ad-hoc patient specific replica will be fabricated, to simulate real surgical cases. The aim is to obtain a patient-specific demonstrator of the AR platform, allowing for a complete in-vitro quantitative and qualitative evaluation of the potentialities and limits of the proposed approach.

Expected Results: deliverables e milestones
DELIVERABLES

- D3.1 Report on the AR software framework for planning and guidance (Task 3.3 - 15 month)
- D3.2 Report on fabrication strategies for physical simulators for in-vitro test (Task 3.4 - 15 month)
- D3.3 Final reporting on in-vitro test (Task 3.5 - 31 month)

MILESTONES

- M3.1 Specification for AR planning & guidance (Task 3.1 - 3 month)
- M3.2 Specification for surgical simulations (Task 3.2 - 3 month)
- M3.3 AR software framework for planning developed (Task 3.3 - 7 month)
- M3.4 First surgical simulator fabricated (Task 3.4 - 12 month)
- M3.5 Final demonstrator of AR software framework for planning and guidance (Task 3.3 - 15 month)
- M3.6 Conclusion of in-vitro test (Task 3.5 - 30 months)
- M3.7 In-vitro data collection concluded (Task 3.6 - 30 month)

Timing:
30 months (1:30)

Total cost of the objective:
255619,6 €

List of activities envisaged under the Operational Objective:
Activity no. 3.1 - Name: Specification for AR planning & guidance - Cost: 13801,63 €

Activity no. 3.2 - Name: Specification for in-vitro set-up - Cost: 7801,63 €

Activity no.3.3 - Name: Development of the AR software framework for planning and guidance - Cost: 19482,4 €

Activity no.3.4 - Name: Implementation of the physical simulators for in-vitro test - Cost: 29379,88 €

Activity no.3.5 - Name: In-vitro test - Cost: 141077,03 €

Activity no.3.6 - Name: In-vitro data collection - Cost: 44077,03 €

Activity no. 3.1 - Name: Specification for AR planning & guidance

Within this activity, the specifications of the dedicated planning and guidance software framework for AR-guided cryoablation will be defined so as to suit to the clinical requirements. The definition of the virtual content that is intended to aid the surgeon throughout the procedure will start from the decomposition of the addressed intervention into surgical sub-tasks (this particular sub-task has been already accomplished by the UNIPI team during the ongoing H2020 VOSTARS project). Therefore, the surgical sub-tasks, within a standard cryotherapy procedure, that could benefit from AR visualization modalities provided by the HMD, will have to be analyzed and modelled. These sub-tasks will come out from the specific surgical needs identified by UO1, in cooperation with the technical partners UO2.

Example of a prototype of an AR system for Hip Arthroplasty developed by RO2. Two "screenshots" of the Hip Arthroplasty, showing the virtual user interface the virtual anatomy in two different configurations: the visualization of the bones, pelvis, and preoperative planning (left), with the muscles hidden (deactivated); and the visualization of the complete virtual content (right). During the project we will extract specifications for the target intervention starting from the group previous experience in AR simulation and navigation.

Tools/equipment:
Workstation/laptop to collect the clinical requirements and to write down the needed documentation.

Human resources:
Staff (full time person month)

UNIPI: Engineer Senior Researcher: 0.42 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Orthopaedic Resident Surgeon 2 p.m
UNIPI: Senior PhD Biomedical Engineer 1,68 p.m

Total Personnel (full time person month) 4,10

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

MILESTONES
- M3.1 Specification for AR planning & guidance (Task 3.1 - 3 month)

Timing: 3 months (1:3)

Activity no. 3.2 - Name: Specification for in-vitro set-up

Within this activity, the specifications for the in-vitro set up will be established. The set-up comprises the patient-specific replicas of the bony structures (healthy and tumoral) to be treated and, more broadly, the experimental workflow to be followed during the in-vitro tests in terms of steps and tools to be used. The experimental workflow will be compliant with the software requirements defined within activity 3.1. The materials of the anatomical replica will be established, both for the bony structures and for the surrounding soft tissues.The rigid part of the mannequin will also comprise the rigid support for the template marker (i.e., image target for the Vuforia tracking engine). These particular sub-tasks have been already accomplished by the UNIPI team during the ongoing H2020 VOSTARS project. A methodology for streamlined and quick production strategy will be decided. The in-vitro set-up will have to comprise also the replicas of the cryoprobes (i.e., kirschner wires) that will be used during the simulated procedure with the aid of the commercial AR HMD (i.e., the Microsoft Hololens). During this task the protocol of the in-vitro study will be also defined, establishing criteria for the evaluation of the procedure success and defining a structured questionnaire for collecting surgeons' opinion.

Tools/equipment:
Workstation/laptop to collect the requirements and to write down the needed documentation.

Human resources:

Staff (full time person month)

UNIPI: Engineer Senior Researcher: 0.15 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

UNIPI: Senior PhD Biomedical Engineer 1.68 p.m

Total Personnel (full time person month) 1,83

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

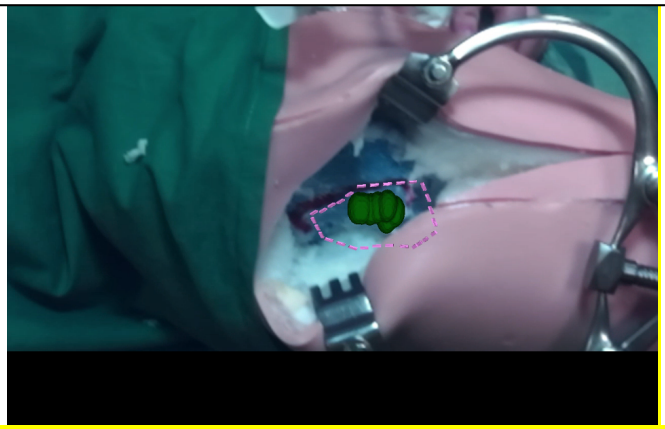
MILESTONES
- M3.2 Specification for surgical simulations (Task 3.2 - 3 month)

Timing: 3 months (1:3)

Activity no. 3.3 - Name: Development of the AR software framework for planning and guidance

Within this activity, the dedicated planning and guidance software framework for cryoablation will be developed so as to be compliant to the surgical workflow of a standard intervention of cryoablation in the operating room, as defined within activity 3.1:

- The preoperative planning software will have to be highly configurable and user-friendly. The patient-specific 3D reconstruction of the bone will be generated from the segmentation of preoperative computed tomography (CT) dataset: the DICOM files will be segmented using a semi-automatic segmentation tool. The resulting 3D virtual model of the bone, in the form of an STL file, will be exported to a specific CAD software to layout the rigid parts and separate them through color coding between healthy tissue, tumor, surrounding vascular and nervous structures, etc.. During planning, the surgeon will synthetically add to the virtual scene the virtual landmarks (e.g., small circles) representing the ideal target points for the cryoprobes. According to the characteristics of the selected cryoprobe, the planning software will have to simulate the ice ball effect on the target anatomy in order to aid the surgeon in properly selecting the ideal placement and orientation of the probe. To be effective in aiding the surgeon performing the cryoablation, the visualization modalities (i.e. type of virtual content) of the AR software framework will have to provide consistent visual cues for depth perception and spatial awareness within the treatment area. By way of example, the AR visualization modalities, will have to be conceived to aid the surgeon in planning the optimal targeting of the bone to be necrotized while avoiding any damage to the surrounding tissues. Based on RO2 experience, a possible visualization modality could consist of a pair of virtual viewfinders to aid the surgeon at placing and orienting the cryoprobe toward the bone surface as dictated during planning.The first viewfinder, surrounding the target point on the bone surface, could indicate to the surgeon where to place the probe tip. The second viewfinder could aid the surgeon in orienting the probe according to the optimal trajectory.
- The guidance software will be developed using Unity3D (5.6.1f). The MixedRealityToolkit, a collection of C# scripts and Unity components to develop mixed-reality applications, will be used to ease the development of the application. This toolkit allows the user to interact with the virtual content by means of head movements (Gaze), gestures (Air Tap, Bloom, etc.), and voice commands (via Cortana). A virtual cursor will be added to the application to indicate the head/view direction: this interaction through head movements is called Gaze. This particular sub-task has been already accomplished by the UNIPI team during the ongoing H2020 VOSTARS project.



In the figure above, we show an example of an AR visualization obtained within the VOSTARS project to treat surgically hip tumors.

- Once the whole virtual scene will be generated, it will be loaded by the guidance software running on the AR HMD. The guidance software will run on the AR HMD (i.e., the Microsoft Hololens). The guidance software will include also tracking data to update the registration of the virtual content to the real scene. The HoloLens includes a world-facing camera; thus, the optical detection and tracking of a target can be used for real-time registration purposes, with no need for an external tracking system. At this end, in our application, we will use the detection and tracking functionalities offered by the Vuforia SDK. More in particular, we could employ an Image Target: image that Vuforia Engine can detect and track at runtime. The Vuforia Engine detects and tracks the features that are naturally found in an image; these features, extracted from the original image, are stored in a preprocessed database, which can then be integrated in the software application. This database can then be used by Vuforia Engine for runtime comparisons. Once the Image Target is detected, Vuforia Engine will track it as long as it is at least partially visible by the camera. The fundamental attributes for an accurate tracking of an Image Target are good contrast, no repetitive patterns, and wealth of details. Moreover, for near-field applications, a physical printed Image Target should be at least 12 cm in width and of reasonable height.

Tools/equipment:

A dedicated workstation/laptop with proper cpu/gpu will be used to develop the planning framework through the following software tools:

- Semi-automatic segmentation pipeline for the CT-data
- CAD software for drawing the virtual scene
- The configurable and interactive guidance framework will be developed through Microsoft Hololens by using Unity3D (with Vuforia plugin) and the MixedRealityToolkit from Microsoft.

Human resources:

Staff (full time person month)

UNIPI: Engineer Senior Researcher: 1.14 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

UNIPI: Senior PhD Engineer 2.23 p.m; PhD Student Biomedical Engineer 2 p.m

Total Personnel (full time person month) 5,37

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

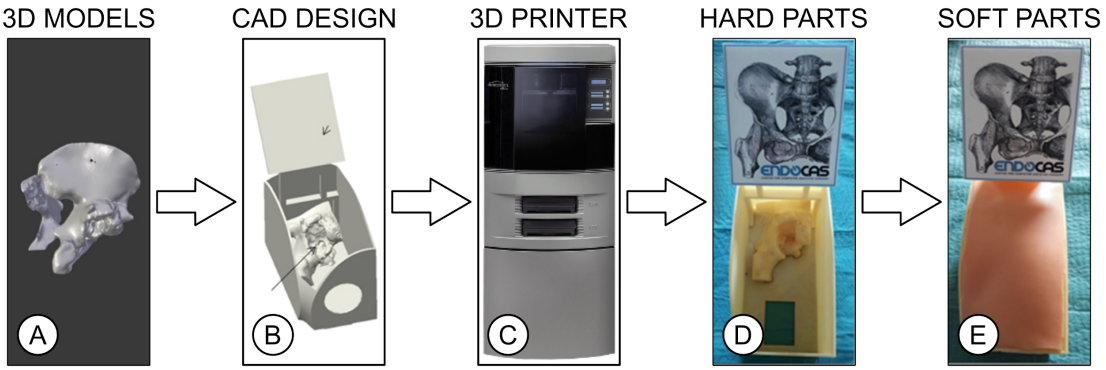
DELIVERABLES
- D3.1 Report on the AR software framework for planning and guidance(Task 3.3 - 15 month)

MILESTONES
- M3.3 AR software framework for planning developed (Task 3.3 - 7 month)
- M3.5 Final demonstrator of AR software framework for planning and guidance (Task 3.3 - 15 month)

Timing: 12 months (4:15)

Activity no. 3.4 - Name: Implementation of the physical simulators for in-vitro test

The development of the simulator will start from the extraction of the anatomical components from real radiological computed tomography (CT) data set. CT images will be processed using a semi-automatic tool, the EndoCAS Segmentation Pipeline, integrated in the open source software ITK-SNAP 1.5. Then mesh optimization stages (artifacts removal, holes filling, simplification, and filtering) will be performed using the open source software MeshLab and Blender.
3D virtual models will be then imported in the Creo Parametric 3D Modelling software, and each physical component will be designed, including a support for the registration target (Vuforia Image Target). This support will be rigidly anchored to the bone synthetic replica to guarantee a precise registration of the virtual content to the real scene.
A 3D printer will be used to turn the 3D CAD models into tangible 3D synthetic replicas made of acrylonitrile butadiene styrene (ABS). This plastic is commonly used for the manufacturing of bone replicas for orthopaedic surgery simulation since it adequately approximates the mechanical behaviour of the natural tissue. Finally, silicone mixtures and polyurethane materials will be used for the manufacturing of the soft parts. The final mannequin will include a replica of the bone embedded in a soft synthetic foam. Moreover, a skin-like covering will be provided for an accurate simulation of palpation and surgical incision.



Example of the steps involved in the development and manufacturing of the physical components of a simple simulator for testing an AR application devoted to Hip Replacement: (A) the 3D model of the bones as generated from the CT dataset of the patient; (B) the CAD design for 3D printing, including the acetabulum and the support for the Image Target; (C) the 3D printer Dimension Elite; (D) and (E) the hard and soft components (respectively) of the simulator, including the Vuforia Image Target placed on top of an ad hoc support.

Tools/equipment:
A workstation/laptop
3D printer (already available)
Lab equipped with instrumentation for the fabrication of the simulators

Human resources:
Staff (full time person month)
UNIPI: Engineer Senior Researcher: 0.11 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)
UNIPI: Senior PhD Engineer 1.8 p.m; Engineer Phd Student 5 p.m

Total Personnel (full time person month) 6,91

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones
DELIVERABLES
- D3.2 Report on fabrication strategies for physical simulators for in-vitro test (Task 3.4 - 15 month)

MILESTONES
- M3.4 First surgical simulator fabricated (Task 3.4 - 12 month)

Timing: 12 months (4:15)

Activity no. 3.5 - Name: In-vitro test

Both Orthopedic surgeons and Resident Orthopedic surgeon will be enrolled in this in-vitro test study. The functionalities offered by the developed AR software framework will be tested simulating the surgical workflow, including the preoperative planning phase and the surgical intervention. Subjects enrolled in the study will be asked to plan the optimal targeting of the bone to be necrotized while avoiding any damage to the surrounding tissues. Then during the simulated surgical intervention, subjects will be asked to place and orient the cryoprobe replica (i.e kirschner wires) toward the bone surface as dictated during planning, with the aid of the AR guidance. The AR view will show the simulated effect of the ice-ball. At the end of the intervention, the accuracy of the

simulated intervention will be evaluated by measuring the deviation of the cryoprobe replica position/orientation from the planned one. The protocol for the accuracy measurement will be defined in the activity 3.2 and could include the use of a 3D optical scanner for the acquisition of the cryoprobe replica position/orientation. Likert questionnaire could be administered to surgeon at the end of the simulated intervention.

Tools/equipment:
3D optical scanner; HMD; PC; in-vitro set-up fabricated during the activity 3.4.

Human resources:

Staff (full time person month)

AUOP: Orthopedic Surgeon: 0.97 p.m
UNIPI: Engineer Senior Researcher: 6.03 p.m

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

AUOP: Resident Orthopedic Surgeon 6 p.m
UNIPI: Senior PhD Engineer 12 p.m; Engineer Phd Student 16 p.m

Total Personnel 41

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

DELIVERABLES
- D3.3 Final reporting on in-vitro test (Task 3.5 - 31 month)

MILESTONES
- M3.6 Conclusion of in-vitro test (Task 3.5 - 30 months)

Timing: 19 months (13:31)

Activity no. 3.6 - Name: In-vitro data collection

Results of in-vitro trial will be carefully collected according to the protocol defined in task 3.2. Collected data will be both qualitative (likert questionnaire) and quantitative (i.e accuracy).

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities

Human resources:
Staff (full time person month)

UNIPI: Engineer Senior Researcher: 6,03
R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

UNIPI: Senior PhD Engineer 2.4 p.m; Engineer Phd Student 4 p.m

Total Personnel (full time person month) 12,43

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

MILESTONES
- M3.7 In-vitro data collection concluded (Task 3.6 - 30 month)

Timing: 19 months (13:31)

Operational Objective 4 (OO4)

Name: DATA ANALYSIS (RO2)

Description of the operational objective:

This operational objective will be devoted to the statistical analysis of the clinical data and in-vitro experimental data collected in the O.O.2 and O.O.3.
Statistical analysis will be performed using IBM SPSS Statistics which is already used by the UNIPI team for on-going analysis of data from different studies.

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

DELIVERABLES

- D4.1 Final report on clinical results analysis (Task 4.1 - 36 month)
- D4.1 Final report on in-vitro results analysis (Task 4.2 - 36 month)

MILESTONES
- M4.1 Conclusion of clinical data analysis(Task 4.1 - 36 month)
- M4.2 Conclusion of in-vitro data analysis (Task 4.2 - 36 month)

Timing:
23 months (14:36)

Total cost of the objective:
22179,7 €

List of activities envisaged under the Operational Objective:

Activity no. 4.1 - Name: Analysis of clinical data - Cost: 11227,77 €

Activity no. 4.2 - Name: Analysis of in-vitro tests - Cost: 10951,93 €

Activity no. 4.1 - Name: Follow up and Analysis of clinical data

Each enrolled patient will undergo to a 12 month follow up, during the definition of the clinical trial specification also the timing of the follow up will be defined in order to reinforce the clinical data outcome and enrich the data collected.
All the quantitative variables will be described by their mean, median, standard deviation and the IQR (interquartile range).
The central tendencies of questionnaire results will be summarized by using median, with dispersion measured by interquartile range.
Correlation among categorical variables will be assessed by the chi-quadro or Fisher exact test. Significance of the estimations will be represented by their P-values.
Missing data will be replaced using conditional means or a regression imputation approach. 5-10% will be considered the cut-off point for missing values.

Tools/equipment:
IBM SPSS Statistics software, PC

Human resources:
Staff (full time person month)

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)
UNIPI: Senior PhD Engineer 2.1 p.m; Engineer Phd Student 0.5 p.m

Total 2,6 p.m

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

DELIVERABLES

- D4.1 Final report on clinical results analysis (Task 4.1 - 36 month)

MILESTONES
- M4.1 Conclusion of clinical data analysis(Task 4.1 - 36 month)

Timing:

23 months (14:36)

Activity no. 4.2 - Name: Analysis of in-vitro data

All the variables will be described by their mean, median, standard deviation and the IQR (interquartile range).
Correlation among categorical variables will be assessed by the chi-quadro or Fisher exact test. Significance of the estimations will be represented by their P-values.

Tools/equipment:
IBM SPSS Statistics software, PC

Human resources:
R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

UNIPI: Senior PhD Engineer 1.13 p.m; Engineer Phd Student 2 p.m
Total: 3,13

Subcontracts: No need for subcontracts

Expected results: Deliverables and/or Milestones

DELIVERABLES
- D4.1 Final report on in-vitro results analysis (Task 4.2 - 36 month)

MILESTONES
- M4.2 Conclusion of in-vitro data analysis (Task 4.2 - 36 month)

Timing:
23 months (14:36)

ALLEGATO B

BANDO RICERCA SALUTE 2018

The project includes clinical trial phases : YES

If YES specify
type of study: prospective, randomized, controlled, three arms, monocentric clinical trial

Pre trial phase (if applicable) NO

If the project provides for the start-up of activities, clinical trial phases must be submitted to the relevant ethics committee for a positive opinion when the agreement is signed

The project includes animal testing phases: **NO**

If the project involves animal testing phases, it is necessary to submit, at the conclusion of the agreement, the authorization of the Italian Ministry of Health according to art. 31 of Decreto Legislativo 26 del 4/3/2014.

Description of the activity carried out by the RO participating in the project pursuant to art. 4 of the call for proposals, specifying whether the participating ROs carry out an additional activity or whether they contribute to the activities listed above.

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SECTION 4 – PROJECT SPECIFICATIONS IN RELATION TO THE SELECTION CRITERIA

A) Scientific and technical quality of the proposal
Scientific novelty, scientific merit and quality of approach

Cryoablation has already been used as palliative treatment or as adjuvant therapy for treating various tumors, including those of the kidney, liver, prostate, lung and musculoskeletal tumors. However, the use of cryoablation as local adjuvant for the treatment of Giant Cell Tumor (GCT) and benign aggressive bone tumors has not been demonstrated as yet and there appear to be no studies, to this day, that have evaluated its efficacy in open surgery. This project addresses this gap in the literature with a clinical study on image-guided cryoablation in oncologic orthopedic open surgery aimed at proving the advantages of the cryoablation over standard adjuvant techniques. The scientific impact and novelty of our proposal will be further strengthened by the in-vitro testing of new highly interactive modalities for augmented reality (AR)-based planning and guidance devoted to cryotherapy.

Moreover, the in-vitro assessment of such innovative wearable AR platform for surgical planning and guidance will pave the way to the definition of a novel and reliable solution for the intraoperative navigation of cryoablation procedures. Our scientific hypothesis is that such AR-based platform, used as aid in navigated cryotherapy, maximizes the synergistic effect of the multiple cryoprobes configurations on the target bone in percutaneous or open procedures. The purpose of the planned research is twofold: to lay down the technical specifications that an ideal planning and guidance AR framework should have to guarantee safety and accuracy in cryoablation procedures, and to design the most suitable AR visualization modality for the guidance of each sub-task involved. After the project conclusion, the smooth translation of the developed AR approach to routine clinical practise will be made possible thanks to the implementation of new AR HMDs specifically dedicated to their use inside the operating room. In line with this ambition, the RO2 is currently coordinating a EU project devoted to the development of a completely new AR HMD to be used as reliable and ergonomic surgical navigation tool (VOSTARS - H2020 Call ICT-29-2016 G.A. 731974 see http://www.vostars.eu).

B) Level of innovation:

From the clinical standpoint, the present project paves the way for the following innovations:

- clinical adoption of cryoablation as local adjuvant in patients affected by GCT after intralesional surgery, to improve the clinical outcomes, reducing the local recurrence of the disease. Standards surgical procedure and protocols consists in curettage (intralesional surgery) or resection (marginal/wide surgery). Curettage is done through a large cortical bone window with the purpose to remove all the visible tumor. Local adjuvants agents (i.e. phenol, alcohol and cement) are commonly used to reduce the incidence of local recurrence. Cryotherapy could be used as a new type of adjuvant therapy the allows reducing the intraoperative bleeding thanks to its "solidifying" effect and minimizing the risk of local recurrency.
- clinical adoption of AR technologies for the preoperative planning of the surgical treatment of

GTC, and in future also of other orthopaedic interventions.
- future clinical adoption of AR technologies for the intraoperative guidance of cryoablation procedures.

From the technical standpoint the present project paves the way for:
- development of protocols for the development of innovative AR frameworks for the surgical planning and surgical guidance of cryoablation procedures,
- development and diffusion of new standards for the in-vitro testing of AR technologies for orthopedic surgery.

C) Reliability of applicants:

The collaboration between medical and technical partners and an interdisciplinary approach will allow the consortium to address all the challenges related to the clinical assessment and to the development and use of the innovative AR-based planning and guidance framework and it will ensure the overall validity and reliability of the project results.

1) The P.I. is a worldwide expert in musculoskeletal tumors. He has been the main researcher or team member of 8 major research programmes of the Council for National Research and the Italian Ministry of Health, and is responsible for 29 current IOR research projects, mainly regarding tumour treatment and surgery. He was also involved in the development programme and patenting of three different prosthetic systems. He is a member of the Permanent Board Commission of the Italian Society of Orthopaedics and Traumatology to the Ministry of Health and the Higher Health Institute on the "Regulation on Bone Grafts and their Substitutes" and of the Commission on "Staminal Cells and Tissue Engineering in Orthopaedics". He is also a member or honorary member of 13 international societies, at several of which he served as President, Vice-President or Member of the Board. He is also on the Editorial Board of five international journals. From 2016 he is chief of the 2nd Orthopedic and Traumatology Division of the University of Pisa. The 2nd Division of Orthopedics and Traumatology of the University of Pisa, represents a center of reference at national level for the treatment of musculoskeletal tumors. The Clinic also performs surgical procedures dedicated to non-oncologic patients, reconstructive and arthroscopic surgery of hip, knee, ankle, shoulder, elbow and wrist, total replacement of the hip, the knee and the shoulder. Surgical treatments of adolescent vertebral deformities (scoliosis and spondylolisthesis) and degenerative diseases of the adult spine (scoliosis, vertebral stenosis, degenerative spondylolisthesis) are also performed.
The 2nd Orthopedic division has 18 ordinary beds and 2 surgical rooms. In the surgical rooms, there are all the facilities to perform oncologic and non-oncologic surgery including surgical instrumentations and c-arm fluoroscopy. The Clinic also manages trauma patients and traumatological urgencies. The Trauma ward has 14 beds and one surgical Room with all the facilities to perform this kind of surgery.
The 2nd Orthopedics and Traumatology Division has a dedicated ambulatory for oncologic, non-oncologic and trauma patients and it is dedicated to the postoperative controls of patients.
The Clinic is part of a large Universitary Hospital AUOP that have all the facilities for a complete management of the oncologic Patients such as for : diagnostic phase (x-ray, CT, MRI, PET, bone scintigraphy ...); the histologic tissue analysis (e.g., biopsy under x-ray or CT control and pathological anatomy examination..); the preoperative preparation (e.g., embolization of the tumor mass, premedications, chemotherapy …); the execution of the surgical procedures with a multidisciplinary team composed by orthopedic surgeons, vascular surgeons, abdominal surgeons, thoracic surgeons; the postoperative phase (e.g., intensive care unit, patients follow-up, chemotherapy, radiotherapy).

2) Department of Information Engineering – University of Pisa
The Department of Information Engineering is recognized by the Italian Ministry of University

and Research as a Department of Excellence that funded new multidisciplinary CrossLabs, one of which dedicated to AR.
Vincenzo Ferrari, the scientific leader of the Research Organization 2, is the scientific coordinator of EndoCAS, Centre of Excellence for Computer Assisted Surgery. EndoCAS was founded with MIUR funds (Ministerial Decree of 17 October 2003, prot. n. 193/2003) thanks to the call "co-financing Centres of Excellence, Bando 2001."
The centre consists of two buildings (EndoCAS-Research and EndoCAS-Education) close one to another.
The mission of EndoCAS-Research is to develop breakthrough technologies based on engineering and information technologies to improve the current surgical procedures and reduce their invasiveness mainly by means of an optimal use of medical imaging.The research areas addressed by the Centre are:
-Development of segmentation software for the generation of patient specific 3D models;
-Surgical navigation systems for mini-invasive treatments;
-Augmented Reality for surgical guidance of for hybrid surgical simulators;
-Surgical simulators development;
-Surgical simulators validation.
EndoCAS applies computer assisted surgery (CAS) systems to demonstrate their effectiveness and encourages their market exploitation, offers analysis of the effectiveness and cost-benefit ratio and validation of both commercial and custom-made systems.
EndoCAS Research has two laboratories for research and development, an experimental operating room used for in-vitro testing of prototypes, an electronics laboratory and a laboratory equipped for the fabrication of surgical simulators with 3D printers. Among the instrumentations already available at EndoCAS there are several commercially HDMs (Hololens, Lumus, Vuzix, eMagin).
At EndoCAS-Research a research team of engineers and computer scientists permanently works in synergy with physicians (orthopedic surgeons, general and vascular surgeons, thoracic surgeons and radiologists). Surgeons carry out research activities either at the center or in their own departments, for the definition of the technologies specification, and their iterative testing starting from in vitro-study to clinical trials.
The research group has extensive experience in the management of national (including also two projects founded by the Tuscany Region, see http://www.valvetech.it/index.php and UltraVista project POR CREO 2014-2020) and international research projects (see http://www.endocas.unipi.it/research/projects/), both as a coordinating unity and as a project partner. Vincenzo Ferrari is currently the PI of the European Project VOSTARS (H2020 Call ICT-29-2016 G.A. 731974 see http://www.vostars.eu) devoted to the development of an innovative hybrid HMD for Video and Optical See Through Augmented Reality surgical system.

The EndoCAS research team, coordinated by Vincenzo Ferrari, has already been successfully collaborating with the AUOP orthopaedic surgeons from 2008 for the development of:

- patent protected solutions for the intraoperative guidance of orthopedic surgical interventions,
- AR based navigation systems,
- preoperative planning with 3D virtual model and synthetic bone replicas,
- physical and hybrid simulator for surgical simulations.

D) Technical validity and economic viability of the project:

Technical viability

The project is based on general and specific skills of the partners involved, on consolidated experience acquired during previous and ongoing research projects, and preliminary clinical results.

Indeed, the 2nd Orthopedic Division of AOUP has already performed a pilot study including 143 cases of musculoskeletal tumors treated with cryotherapy. Diagnosis were: in 38 patients (26,6%) metastases from carcinomas, in 16 patients (11,1%) angiomas/aneurismal bone cyst, in 22 patients (15,4%) musculoskeletal tumor low grade, in 2 patients (1,4%) fibromatosis, in 63 patients (44,1%) musculoskeletal benign tumors (principally giant cell tumor-TCG),in 2 patients (1,4%) osteosarcomas (as palliative therapy). In all 63 patients affected by CGT, cryotherapy was used as adjuvant therapy to open surgery. Preliminary data suggest that cryotherapy is highly effective in the lesions, especially those located in the femur and tibia.
From the technical side, the RO2 has already been successfully collaborating with surgeons from AUOP (orthopaedic surgeons, neurosurgeons, vascular surgeons) and maxillofacial surgeons from Ospedale S. Orsola Malpighi in Bologna, for the development of innovative AR based surgical navigation systems, of dedicated preoperative planning framework featuring 3D virtual model and synthetic bone replicas {Badiali, 2014 #11130} {Cutolo, 2016 #12045} {Cutolo, 2016 #11092}, and the implementation of physical and hybrid surgical simulators {Carbone, 2011 #5699;Condino, 2011 #7162;Viglialoro, 2014 #7358;Parchi, 2016 #12252;Parchi, 2016 #7479;Viglialoro, 2016 #7593;Condino, 2018 #12132;Turini, 2018 #11568}.

Economic viability

From and economic point of view, the results of the clinical trials will demonstrate that the proposed approach allows a reduction of the need for reintervention, that reflects in reduced cost for the whole health care systems.
As to the economic viability, in the R&D projects, the main costs are personnel costs. The estimate of the person months to be employed is always uncertain owing to the innovativity of the technological solutions proposed that require careful exploration of multiple alternatives. However, such estimate is all the more reliable when it can be based on extensive project experience, with the same staff or staff with the same level of expertise. The planned expenditure is based on the experience gained by the two partners in previous research projects. In fact, these partners have been working on national and European R&D projects for some time, and currently participate as partners and/or lead partners in about five other projects.
On the basis of consolidated experience of collaboration between the two Partners, a careful planning of the activities and resources necessary for this project has been made, also taking into account the time and resources demanded for the development of similar AR platform and surgical simulators in the past.

E) Ability of the project to create good network relationships:

The project will strongly contribute to strengthen Tuscany research and industrial capacities in those sectors directly involved into the research and development of novel interactive AR applications primarily in the healthcare sector. Given the above, and considering the new challenges that have arisen from the evolution of Industry 4.0, we expect that our project is bound to have a relevant impact to the establishment of a sustainable competitive ecosystem of Tuscan solution providers in the field of image-based planning and assistive technologies.
From a medical perspective, the results of the project will be disseminated also in other Hospitals in Tuscany and outside Tuscany, thanks to the participation to national and international medical conferences and to the use of patient-specific simulators for demos of the proposed technology/approach.

F) Relevance of the project:

We believe that our project is coherent with the regional sectoral policies. As highlighted by the Multi-

year Guidelines on Research and Innovation 2011-2015, the regional RTDI strategy identifies among the macro-areas of intervention: the support to regional high-tech sectors and the support to health-care research. Both the listed sectors are covered by our project.
We also believe that our research project perfectly fits to the strategy for the 2014-2020 programming period particularly focused on the linkage of research and development programs with
smart specialisation initiatives as ICT/photonics.

The project is consistent with the purpose of the call. In fact, the results of this project will be of paramount relevance for indicating cryotherapy as a promising methodology for the treatment of rare tumors as GCT. In this way, cryoablation will be selected as an alternative therapy to standard surgery. We expect that these significant clinical outcomes are bound to be improved if followed by the development of an ad-hoc preoperative surgical planning platform with an highly interactive AR interface.

The project takes into account the requirements of the Italian Ministry of Health concerning the risk assessment and the reduction of costs for the Regional Healthcare System (SSR). Currently. cryotherapy is conventionally used for palliative treatment and, only occasionally, as definitive treatment of musculoskeletal tumors as fibromatosis, osteoid osteoma or angiomas. Early data support new surgical indications for cryotherapy in orthopaedic oncology with relevant results in terms of clinical outcomes. Moreover, the in vitro pilot-study will pave the way to the definition of a disruptive and reliable AR platform for the intraoperative navigation of cryoablation in orthopedic oncology, and more broadly for any surgical procedure involving needle or trocar insertion with an open or percutaneous approach with important advantages in terms of patient safety and reduction of exposure to ionizing radiation for the operators.