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HyperProbe consortium: innovate tumour neurosurgery with innovative photonic solutions

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ABSTRACT

Recent advancements in imaging technologies (MRI, PET, CT, among others) have significantly improved clinical localisation of lesions of the central nervous system (CNS) before surgery, making possible for neurosurgeons to plan and navigate away from functional brain locations when removing tumours, such as gliomas. However, neuronavigation in the surgical management of brain tumours remains a significant challenge, due to the inability to maintain accurate spatial information of pathological and healthy locations intraoperatively. To answer this challenge, the HyperProbe consortium have been put together, consisting of a team of engineers, physicists, data scientists and neurosurgeons, to develop an innovative, all-optical, intraoperative imaging system based on (i) hyperspectral imaging (HSI) for rapid, multi-wavelength spectral acquisition, and (ii) artificial intelligence (AI) for image reconstruction, morpho-chemical characterisation and molecular fingerprint recognition. Our HyperProbe system will (1) map, monitor and quantify biomolecules of interest in cerebral physiology; (2) be handheld, cost-effective and user-friendly; (3) apply AI-based methods for the reconstruction of the hyperspectral images, the analysis of the spatio-spectral data and the development and quantification of novel biomarkers for identification of glioma and differentiation from functional brain tissue. HyperProbe will be validated and optimised with studies in optical phantoms, *in vivo* against gold standard modalities in neuronavigational imaging, and finally we will provide proof of principle of its performances during routine brain tumour surgery on patients. HyperProbe aims at providing functional and structural information on biomarkers of interest that is currently missing during neuro-oncological interventions.

Keywords: HyperProbe, hyperspectral imaging, neuronavigation, intraoperative imaging, tissue optics, cancer imaging.

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1. INTRODUCTION

Every year, an estimated 22.6 million patients suffer from neurological disorders or injuries that warrant the expertise of a neurosurgeon, of whom 13.8 million require surgery. An important part of these neurosurgeries needs intraoperative identification of brain functional areas in order to avoid any worsening of patient's neurological status[1,2]. Measuring brain functional activity is of paramount importance during neurosurgery, such as in glioma and glioblastoma (GBM) removal, due to the critical needs for surgeons to: (1) differentiate healthy tissues from tumour/pathological ones; and (2) preserve the integrity of the cerebral functions of the patients intra- and post-surgery. For this reason, brain activity stimulation plays a fundamental role in current neuronavigation approaches for localising, identifying and assessing areas of cortical and subcortical functions. Several paradigms of brain stimulation are used intraoperatively, mainly depending on which regions of the cortex are targeted, spanning from cognitive tasks on awaken patients (e.g., for speech and visual functions) to electro-stimulation (e.g., for sensorial and motor functions). The latter can be performed in multiple ways, including direct transcortical and/or subcortical stimulation with probes, as well as indirect stimulation and monitoring of muscular responses via electrodes. However, all these types of stimulations present limitations, such as different degrees of invasiveness, lack of real-time, quantitative information, reduced specificity and sensitivity. Furthermore, current imaging techniques (Figure 1) used to measure brain activity in neurosurgery, either at resting state or during stimulation, are also affected by similar constraints, either (1) being based on static, pre-surgical assessments (e.g., MRI, PET-CT), or (2) for intraoperative modalities (e.g., fluorescence imaging), providing low spatial resolution, low specificity to cerebral functions and limited breadth of information[1-3].

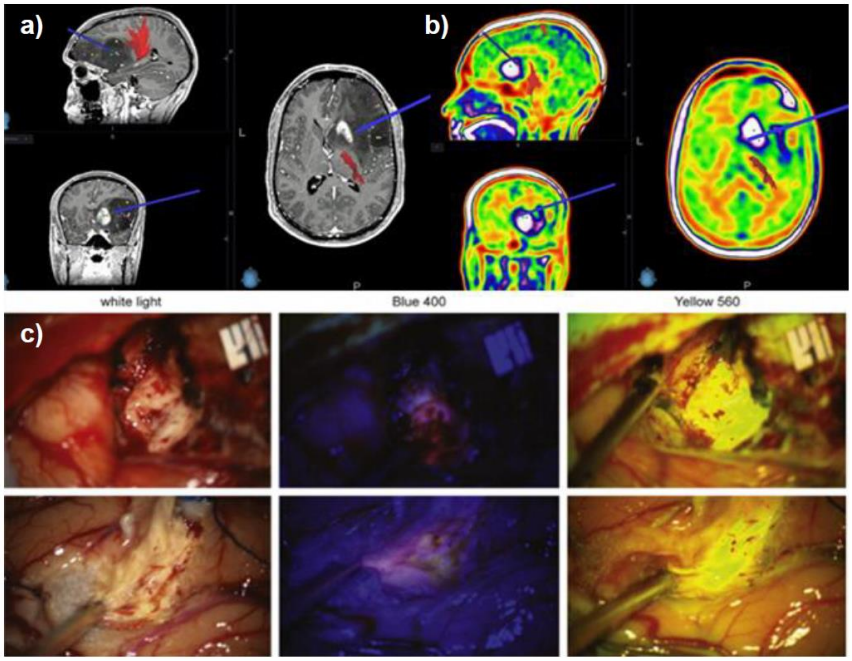

Figure 1. Technologies used for surgical planning and during neurosurgery: a) neuronavigation system based on preoperative MRI tractography; b) PET-CT scan, integrated in the neuronavigation system, for identification of the most metabolically-active areas of the tumour and the peritumoural parenchyma; c) Examples of fluorescence discordance at the tumour border, using 5-ALA (Blue 400) and fluorescein (Yellow 560)[3].

Overcoming the above-mentioned limitations in neurosurgical planning and management will require to transform and advance current clinical practice towards a functional-guided neuronavigation approach that is capable of providing assistance to neurosurgeons in decision-making with a real-time, quantitative and accurate assessment of brain activity intraoperatively. There is an urgent need for new neuronavigation approaches that can be used in parallel with the already available tools, providing real-time, high-resolution, accurate identification of tumour tissue, as well as characterisation and quantification of the functional and structural status of the brain during surgery. Such approaches also need to be coupled with current stimulation paradigms and methodologies to provide a complete and exhaustive monitoring of cerebral activity intraoperatively. To answer this need, we build on previous work from different research groups and created the HyperProbe consortium[4,5], putting together a large and variegated interdisciplinary team of optical and imag-

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ing engineers, physicists, software engineers, and clinicians to develop a novel, all-optical, contactless, intraoperative imaging platform based on hyperspectral imaging (HSI).

1.1 Objectives of the HyperProbe consortium

The HyperProbe consortium started on 1st October 2022 and will evolve over a timeline of five years, funded by the European innovation Council (EIC) and UK Research and Innovation (UKRI). Among its partners are: (1) University of Florence (UNIFI), the project coordinator; (2) Emoled S.r.l; (3) Technical University of Munich (TUM); (4) Université Claude-Bernard Lyon 1 (UCBL); (5) Azienda Ospedaliero-Universitaria Careggi (AOUC); (6) European Institute for Biomedical Imaging Research (EIBIR); (7) Lyon University Hospital (HCL); and (8) University College London (UCL). The consortium has the following objectives, all contributing to the goal of developing and demonstrating efficacy and applicability of a novel device to transform neuronavigation during brain surgery and cortical activity stimulation:

1) Development of a HSI system called HyperProbe to map, monitor and quantify biochemical compounds of interest in brain tissue during neurosurgery and cortical activity stimulation.
2) Industrial upgrade of HyperProbe to a cost-effective, transportable, and compact prototype, that is fully suitable for the neurosurgical room.
3) Characterisation and metrological validation of HyperProbe on optically-realistic brain tissue phantoms.
4) Development of machine learning (ML) and artificial intelligence (AI) algorithms to identify biomarkers of brain activity for *in vivo* imaging with HyperProbe during brain surgery and cortical activity stimulation.
5) Validation of HyperProbe in clinical settings against other surgical imaging standards, such as fMRI (functional MRI) and other optical modalities.
6) Conduction of feasibility studies on the performances of the HyperProbe on patients during glioma surgery and multiple paradigms of stimulation of brain activity, as part of observational, proof-of-concept analysis.

A scheme of the work planned by the HyperProbe consortium over the next five years is summarised in Figure 2.

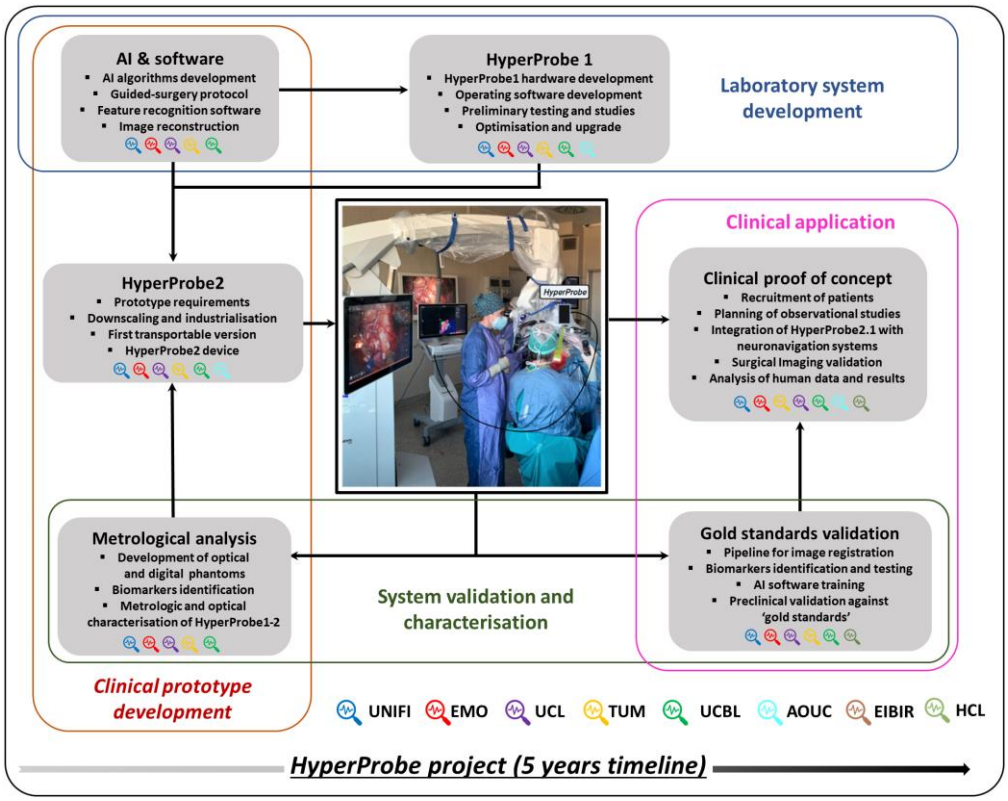

Figure 2. Diagram of the organisation of the HyperProbe consortium and all its scientific tasks and objectives.

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2. THE HYPERPROBE SOLUTION

The HyperProbe system will use the full potential of HSI, i.e., an optical imaging modality capable of acquiring 2D images of a target at multiple, narrow and contiguous wavelength bands in the electromagnetic spectrum, including the near UV-visible (300-700 nm) and the near-infrared (NIR) range (700-1100 nm)[6]. This modality extends the advantages of spectroscopic analysis, by (i) looking at the optical signature of a tissue to extract quantitative information about its chemical composition with high spectral resolution and (ii) providing 2D optical image reconstruction of the interrogated brain tissue. HSI has the capacity to allow users to target and identify specific brain tissue biomarkers in neurosurgery, providing monitoring and assessment of the physiology and pathophysiology of the brain, as well as of the functional and structural status of cerebral tissue[7,8].

2.1 The HyperProbe systems

We plan to firstly design and develop a laboratory-scale, top-grade HSI instrument that enables flexibility in the use of variable numbers and types of wavelengths across the visible and NIR range, as well as utilises cutting-edge technology for illumination, spectral separation, detection of light and image reconstructions. This system will employ a supercontinuum laser (SCL) that emits a broadband light at high power density. The SCL will then be coupled with acousto-optical tunable filters (AOTF) which will modulate the broadband light and separate it in its constituent spectral components. This process will allow us to select any narrow spectral band (with bandwidth down to 1-2 nm) from the broad spectrum of the SCL, modulate its intensity and use it to illuminate a target. The AOTFs are also capable of fast switching between different spectral bands (down to 10-100 μs) so that the target can be illuminated rapidly at different wavelengths sequentially. A high-format, high-resolution imaging camera will then be employed to acquire images of the target at each illuminating spectral band, in order to reconstruct a 3D spatio-spectral dataset, called 'hypercube'. The 'hypercube' contains the full scale of the optical signature of the target and its analysis can provide full characterisation of the morpho-chemical features of the imaged object.

Hyperspectral image reconstruction and analysis will implement AI-based methodologies to reduce the computational burden of the collected data and speed up image acquisition, offering real-time, tailored spectral information specifically optimised to target and accurately quantify biomarkers of interest, including endogenous chromophores, such as: (1) oxy- (HbO_2) and deoxyhaemoglobin (HHb) for monitoring tissue oxygenation, haemodynamics and state of inflammation[6,7]; (2) cytochrome-c-oxidase (CCO) for mitochondrial metabolism and cellular energetics[9-11]; (3) collagen, lipid and water content, for structural and morphological tissue characterisation[12]. Endogenous and exogenous fluorophores could also be targeted via HSI, including: (1) autofluorescent nucleotides (e.g., NADH) and flavoproteins (e.g., FAD) for tissue cellular metabolism[7]; and (2) injected fluorescein, 5-ALA and protoporphyrins, for tumour boundaries localisation, as well as identification and assessment of severity and degree of advancement[13].

The laboratory version of the HyperProbe (HyperProbe1) will be a key first step for calibrating and optimising the performances of the clinical prototypes, such as number/type of wavelengths to be used, and to test the capabilities of the system to target the above-mentioned biomarkers, as well as its biocompatibility and medical safety. This will be done *in vivo* on animal models (mice and rats) and *ex vivo* on fresh surgical biopsies of both healthy and tumour brain tissue (for further information about biopsies studies via HSI, see abstract EB102-64 from Giannoni *et al*.). The HyperProbe1 will also be used to develop the initial version of the software for the data analysis and image reconstruction. Afterwards, the results obtained with the laboratory instrumentations will be used to identify the essential features that allow the expected imaging performances of the final HyperProbe1 lab system, defining in this way the starting point of the clinical prototypes (HyperProbe2 and 2.1).

Once cost-effective and compact solutions have been identified from the results of HyperProbe1, a first transportable prototype (HyperProbe2) will be designed and built to be shared with the other partners for further technical validation, software development, and clinical safety verification. This step will lead to the development of a second and final device, by downscaling and upgrading the initial technology to a fully-working, clinically-adapted prototype (HyperProbe2.1) that is up to clinical safety requirements. HyperProbe2 and 2.1 will be based on lower-cost technological equipment, such as multiple light-emitting diodes (LED). The engineering activities of the final prototypes will be based on aspects of industrial production, applicable regulatory requirements, and assessment of associated risks (including medical safety and biocompatibility), considering the environment and intended use. A depiction of the various steps of the HyperProbe setup and its location in the surgical room is visible in Figure 3.

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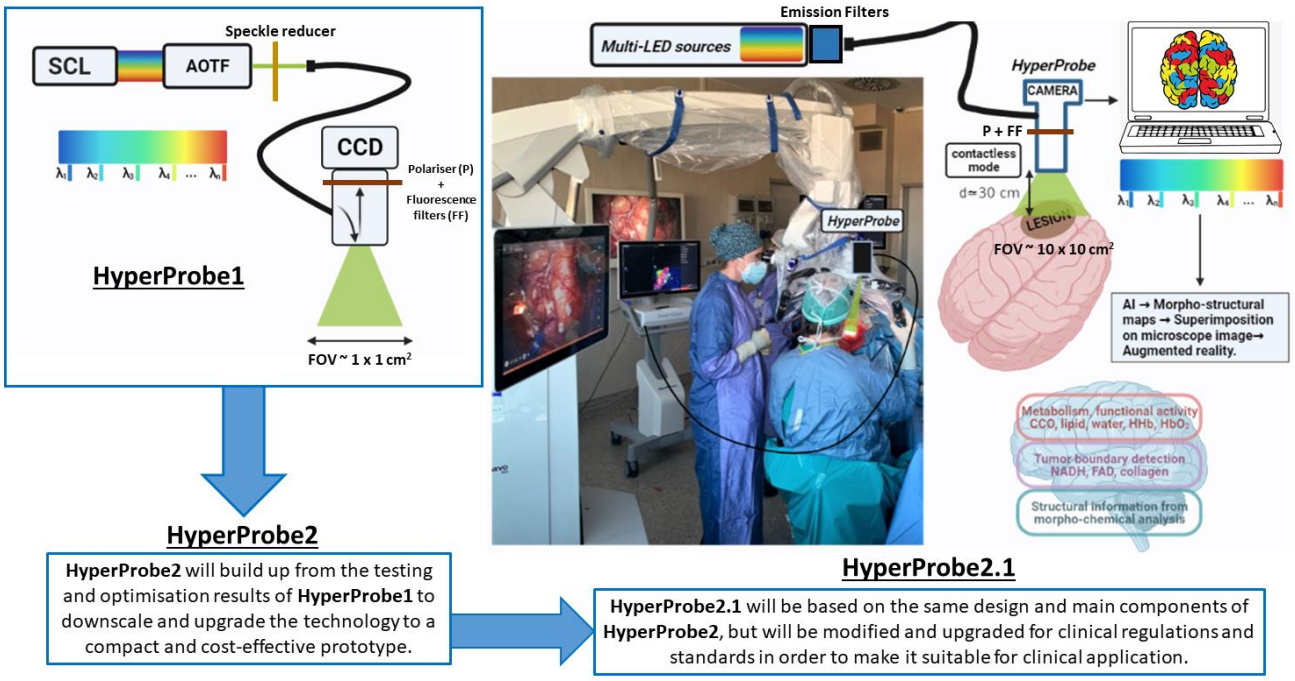

Figure 3. Schematic design of the main HyperProbe devices (HyperProbe 1 and HyperProbe2.1) and the implementation of the final clinical prototype (HyperProbe2.1) in the surgical room.

The HyperProbe devices will take advantage of the application of AI/ML approaches to image reconstruction, data analysis and morpho-chemical features recognition. This represents a novelty in the field, compared to existing and commercially available biomedical HSI cameras and devices, which only rely on simplified methodologies to reconstruct qualitative colour maps of the targets, without providing any quantitative information nor any tissue morpho-chemical characterisation. In order to fully exploit the richness of the HyperProbe data, we will develop an end-to-end trainable deep learning pipeline for image reconstruction and image analysis of the hyperspectral data (for further information, see abstract EB102-55 from Ezhov *et al.*). For image reconstruction we will focus on developing unsupervised (e.g. self-supervised) approaches that can be applied to image reconstruction problems where suitable training data is difficult or cannot be obtained. In these self-supervised learning approaches the supervision tasks are generated from the data itself in order to learn useful feature representations[14].

3. OPTIMISATION, VERIFICATION AND VALIDATION

3.1 Metrological characterisation and validation

A rigorous characterisation of the HyperProbe devices is essential to objectively compare and assess the accuracy of our system and the consistency between the various versions that we will develop. Indeed, we need to make sure that the basics outputs of the instrument (i.e., optical properties: absorption and scattering) are valid in order to quantify accurately the various biomarkers (i.e., concentrations in haemoglobins, water, fat, fluorophores, etc.). To do so, we will use reference optical phantoms with known optical properties to test and refine our instrument to produce accurate quantities[15]. Then, specific phantoms will be developed to specifically test the accuracy of the HyperProbe1 and 2 to retrieve the contrasts of interest. Homogeneous liquid phantoms will be specifically designed to produce the desired contrasts and will aim to be as realistic as possible in terms of optical properties (i.e., by using blood and yeast)[16]. These phantoms will be used more specifically to validate crosstalk between the multiple contrast that we are targeting, which is a known challenge for optical imaging[9] (for more details, see abstract EB102-49 from Caredda *et al.*). A final step will be to develop anatomically accurate phantoms to test the effect of the complex shapes of the brain anatomy and produce a final testing platform for our prototypes. These phantoms, based on 3D printing[17], will be the ultimate tool to assess the performance of HyperProbe in a realistic setting. Finally, we will also develop digital phantoms to help us optimise the parameters of our system during its development (for further information about digital phantoms, see abstract EB102-70 from Lange *et al.*). These phantoms allow us to test various scenarios, both from the point of view of the anatomy and physiology[18].

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3.2 Validation against neuronavigational 'gold standards'

The cross-validation of HyperProbe2.1 against clinical 'gold standards' is essential for this project, which aims at transforming neurosurgery practice. Indeed, any change in the clinical routine should be strongly sustained by evidence that HyperProbe is first able to reproduce the results of the clinical gold standard, and secondly to go beyond these abilities. This process needs firstly biomarkers cross-validation, which in turn also requires the design of automatic image processing pipelines for intra-, pre- and postoperative biomarkers registration. Intraoperative imaging gives access to the curved surface of the exposed brain area, which evolves during brain resection of pathological tissues. This area will be registered with preoperative 3D MRI space, intraoperative electrical brain stimulation and postoperative pathological analysis, using automatic procedures. This process will be conducted on patients using existing intraoperative optical modalities and already validated during clinical studies in patients, i.e., (1) visible and hyperspectral cameras[19]; (2) 5-ALA induced fluorescence spectroscopy[20].

Tumour severity is linked with tissue perfusion, metabolism and tumour cell density. Clinical gold standards for these are pathological analysis, fluorescence surgical microscopy and MRI. In particular, the fluorescence emitted by 5-ALA treated patients is complex and tumour severity is hardly investigated for low-density tumour cell infiltration with clinical standard intraoperative technique[21]. We showed that the spectral shape of the protoporphyrin IX fluorescence signal is closely correlated to pathological status even for low density margins[13], but the extrapolation to spectral imaging is still an open question. We will develop a fluorophore quantification model integrating 5-ALA, induced protoporphyrin IX and endogenous fluorophores. Using pathological analysis as 'gold standard', we will evaluate the relevance of the different fluorophores and the spectral resolution needed. We will also assess microvascularisation optical parameters (e.g., haemoglobin perfusion and oxygenation) against MRI-specific sequences. All these models will then be used with HyperProbe2.1 data in patients. The clinical characterisation of HyperProbe2.1 will be a key point for the fast translation of the models.

4. FUTURE WORK AND EXPECTED OUTCOMES

4.1 Proof of concept of HyperProbe in clinical setting

The clinical application of the project will then be performed in the Neurosurgery Department of HCL and the Neurosurgical Department of the University Hospital of Florence at AOUC. The application of HyperProbe2.1 will be performed during removal of brain malignancies, simultaneously and synergically with already-available tools, such as the neuronavigation system, integrated in the microscope for the fluorescence-guided surgery, the transcranial magnetic brain stimulation (TMS) and the neurophysiological monitoring. The surgical aim is to provide a high-technologically qualified brain surgery to achieve the best postoperative outcome possible for patients, optimising surgical excision of brain tumours and preserving brain functionality, especially in eloquent areas. The application of the HyperProbe device aims at being effective, easily manageable, space-sparing and reproducible in different areas of the brain tumours and parenchyma. Observational studies will be conducted including patients aged between 18 and 80 years old, receiving a diagnosis of brain tumour/brain malignancy, based on the clinical evaluation, radiological imaging, and preoperative data collection.

4.2 Expected outcomes and impact

The results provided by the application and clinical validation of the performances of HyperProbe can significantly impact clinical translation of HSI, and of optical medical devices in general, within surgical practice, which are currently lacking of diagnostic/imaging reliability, breadth of quantitative information, cost-effectiveness, compactness and finally of ease-of-use for neurosurgeons to integrate them with currently available neuronavigation technologies.

The HyperProbe could represent the first exhaustive, multi-biomarker, quantitative optical imaging device used in image-guided neurosurgery and impact the clinical practice by moving it towards functional-imaging based and machine-based, decision-making approaches. These will be centred on objective, accurate functional and structural data on the physiological and pathological status of the brain, in real-time intraoperatively. The cost of the HyperProbe clinical prototype (HyperProbe2.1), which we aim at making in the same order of magnitude of current neuronavigation tools (e.g., surgical fluorescence microscopes), can make the device competitive for neurosurgeons to adopt without unsustainable investments, together with the advantage of being capable of full integration with current surgical instrumentation.

HyperProbe could help neurosurgeons to better analyse the relationship between the tumour/metastases and/or healthy tissue, optimising the tumour removal, and further improving the quality of surgical results. Therefore, we estimate to be

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able to use HyperProbe in around 100 surgical sessions per year. The clinical, observational study will be aimed at using the HyperProbe system intraoperatively in order to understand how it can be synergically used with the already available technologies in the operative field. Our future perspective is the clinical/surgical application of this adjunct. The clinical/surgical benefit of the HyperProbe application will consist of a high-technologically qualified surgery, preserving brain functions and minimising the risk of postoperative neurological impairment.

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