1. Publishable Summary

Summary:

Cancer is the second largest cause of death and morbidity in Europe, with over 3 million new cases being diagnosed each year and can affect anyone – the young and old, the rich and poor, men, women and children. The most effective treatment method for most forms of cancer is early detection followed by surgery. The problem with surgery is that even after the cancerous tissue has been removed, cancers frequently recur. This is a result of incomplete excision of the original cancerous tissue or inadequate clearance of surgical margins. Tumours often fail to be completely excised because the surgeon only has the visual appearance of the tumour and palpation to differentiate malignant from benign tissue. Consequently, there is an urgent clinical and market need for improved tools to help surgeons detect cancerous tissue during surgery.

The aim of the CLI Project is to develop two imaging devices during surgery and to enable surgeons to more accurately resect tumours and thereby reduce the likelihood of post-surgical recurrence. The devices being developed in the Project are:

1. A Specimen Analyser into which the excised tumour material can be placed and imaged to determine if any Cerenkov light is emitted from the margin (at or near the surface of the specimen).
2. A hand-held fiberscope positron detection device to detect and image actively metabolic tumour cell clusters in the surgical cavity.

Both Devices 1 & 2 are surgical devices that are used to detect radiopharmaceuticals during the surgeries such as radio-labelled fluorodeoxyglucose (^{18}F-FDG) within Cancer Patients, and aim to increase future remission levels.
The Specimen Analyser uses a novel molecular imaging technology called Cerenkov Luminescence Imaging (CLI). CLI is based on the recent discovery that Positron Emission Tomography (PET) radiopharmaceuticals (such as ^{18}F-FDG) can be imaged optically. CLI thus combines the advantages of optical imaging (low cost and small form factor) with the power of PET imaging (high diagnostic performance and widespread availability of contrast agents). Importantly, CLI allows molecular imaging devices to be miniaturised sufficiently to be taken into the operating theatre.

The original approach for this project was to take a hand-held fiberscopic version of the CLI technology into clinic for proof of concept and safety evaluation. Several theoretical questions raising consequent practical considerations and sterility challenges presented barriers to exploitation of the extremely low levels of 18F-FDG-emitted Cerenkov light photons. This resulted in the Consortium starting to research other means of detecting ^{18}F-FDG. by detecting positrons for the hand-held, ‘open-surgical’ applications. Thus, the Consortium put forth a the “Betascope” design of a fiber optics based system to image the positrons emitted from the radiopharmaceuticals directly.

From earlier experience in a pre-clinical trial, the build-up and the data acquisition and processing chain of both devices have been modified in the Period. The improved Betascope system and new data acquisition and filtration methods have been implemented in pre-clinical surgeries. Thereafter the ex vivo imaging System 1. and the intraoperative System 2. (Betascope) have been put forward to an early stage clinical trial in large surgery field, open abdominal surgeries. The clinical trial has resulted in obtaining proof of concept and safety data and has wide ranging consequences for the next development steps of Betascope-design direct beta imaging technology-based surgery

devices.

Description of work performed
The Project consisted of several concentrated areas including:

- Work Package 1 – Pre-Clinical Study.
- Work Package 2 – Clinical Trial
- Work Package 3 – Dosimetry evaluations
- Work Package 4 – Prototype Design and Build
- Work Package 5 - Use and Dissemination of Knowledge

During the Second Period of the project, following the recommendations of the review to lift the suspension, appropriate changes to the Design and Build-up and Data Analysis of the Betascope Direct Beta Imaging system have been realized in Work Package 4. In Work Packages 1 and 2, the pre-clinical and the clinical studies have used in part the improved imaging systems (Specimen Analyser and Betascope) and have obtained conclusions that can be cornerstones to further application of radio-guided and ^{18}F-FDG based surgery (both in Work Package 3 and 2). The Project consortium has performed adequate number of pre-clinical surgeries for estimation of clinical dosimetry in large-scale open-abdominal surgeries. Histology and data analysis tools were applied to correlate cellular tumour tissue heterogeneity to observed/imaged heterogeneities in Cerenkov light or positron emission of the excised tumours. The Clinical Trial in open, abdominal surgeries of upper gastrointestinal track has been analysed at 13 patients completed. As a direct result of the Project, several design features have been applied for intellectual property protection as Patent Applications as pursued in Work Package 5, including the full Betascope acquisition chain. Partners in the Consortium have established agreements to exploit these and other foreground of know-how to further develop direct beta imaging in surgery technologies.

Final Results

The results within the Project showed the concept of ^{18}F-FDG based surgery aided by the Specimen Analyser and the Betascope to be viable option both in research and pre-clinical and also in clinical cancer surgery. This is a major result as immediate access to the `contrast agent` exists already for any cancer patient everywhere in Europe.

With the developed prototype devices, the Consortium has performed pre-clinical and clinical studies, established the dosimetric implications and caveats of such radio-guided surgery procedures in previously not reported world-first open abdominal surgery settings. Optimally decreased injected radioactivity for the clinical patients has been determined based on dosimetric implications.

It has been implicated in other clinical trials of LighPoint that the radio guided surgery does not place the necessity of a previous PET(CT) scan of the same patient. This consideration is related to decreasing the total internal absorbed dose by the patient. The second very important reason behind this working model is that in many cases direct tissue imaging at surgery could and has identified many later histologically confirmed uptake locations of the radiopharmaceutical in tumors. These uptake sites could not be identified or even hinted by any PET scan given their small size and very small but still detectable amount of uptake. The three orders of magnitude differences between whole-body PET sensitivity and resolution and the sensitivity of either the CLI Specimen Analyser but even more that of the Betascope. Indeed, amounts of radioactivity uptake as low as 300 Bq could be identified in live pancreatic cancer tissue during a 60 seconds' acquisition time with

the Betascope while no uptake on previous PET scans was visible in the patient. This means that either positive or negative predictive value of whole-body PET images is meant for wholly different use in diagnostics than the immediate surgery application of much more sensitive instruments. Therefore, a further collateral radiation burden of compulsory PET(CT) scan be taken away from the patients.

Decreased need for the injected radiopharmaceutical activity amount further means radio-guided surgery to be more on the cost- and risk-effective side.

It has been proven in the Project Dosimetry Work Package that a reasonable amount of clinical surgeries (very conservatively estimated more than 100 yearly) can be offered to the cancer patient and still do not represent a dosimetric outlier for clinical operating personnel. Waste production during these radio guided surgeries has been proven to be absolutely below the `declared free range` and does not represent any immediate or late increased public risk.

In clinical studies, pancreatic and gastric cancer metastatic foci were imaged by direct beta imaging Betascope both in vivo and immediately ex vivo during and within surgery. It has also been shown that a very high sensitivity is offered by ex vivo direct beta imaging even in the immediate vicinity of the large gamma background source of the patient. Conditions of application for tumour margin in vivo imaging have been set with Betascope. The feasibility of imaging tumour margin using direct positron features has been shown.

An unexpected high relevance has also been established in ex vivo immediate Betascope measurements on excised tumour margins and tumour parts. This means bringing clinical decision-making more based on metabolic tissue properties than hand palpation or visual cues for the operating surgeon.

Cerenkov Imaging with the ex vivo Sample Analyser system has been turned out as the highest immediate importance result. During the project, CLI-based Investigational Medical Device has been turned to a clinical, CE-marked commercial device product. Furthermore, sales of this device (branded as LightPath) have been acquired in the UK and US markets. This major achievement is clearly showing that the results of the project are turning into medical devices benefitting cancer patients and cancer surgeons in a variety of ways from ex vivo breast cancer margin detection to in vivo metastasis imaging.

For more information on the CLI project, please visit our website or contact us directly.
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CLI Project
Optimization of Cerenkov Luminescence Imaging for Image-Guided Cancer Surgery
http://www.clioproject.eu/

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Partners: