Leiden University Medical Center

CHDR
Centre for Human Drug Research

Image-guided Surgery

Helping surgeons visualise tumour cells in living colour

Developed by surgeons, biomathematicians, and researchers, image-guided surgery uses fluorescent markers to help the surgical oncologists ‘see’ the tumour in real time. This innovative, powerful technique significantly increases the outcome of tumour-resection surgery.

Practical answers to important research questions

What is the optimal dose for administering the labelled molecule in order to accurately visualise the tumour against background (i.e. healthy) tissue?

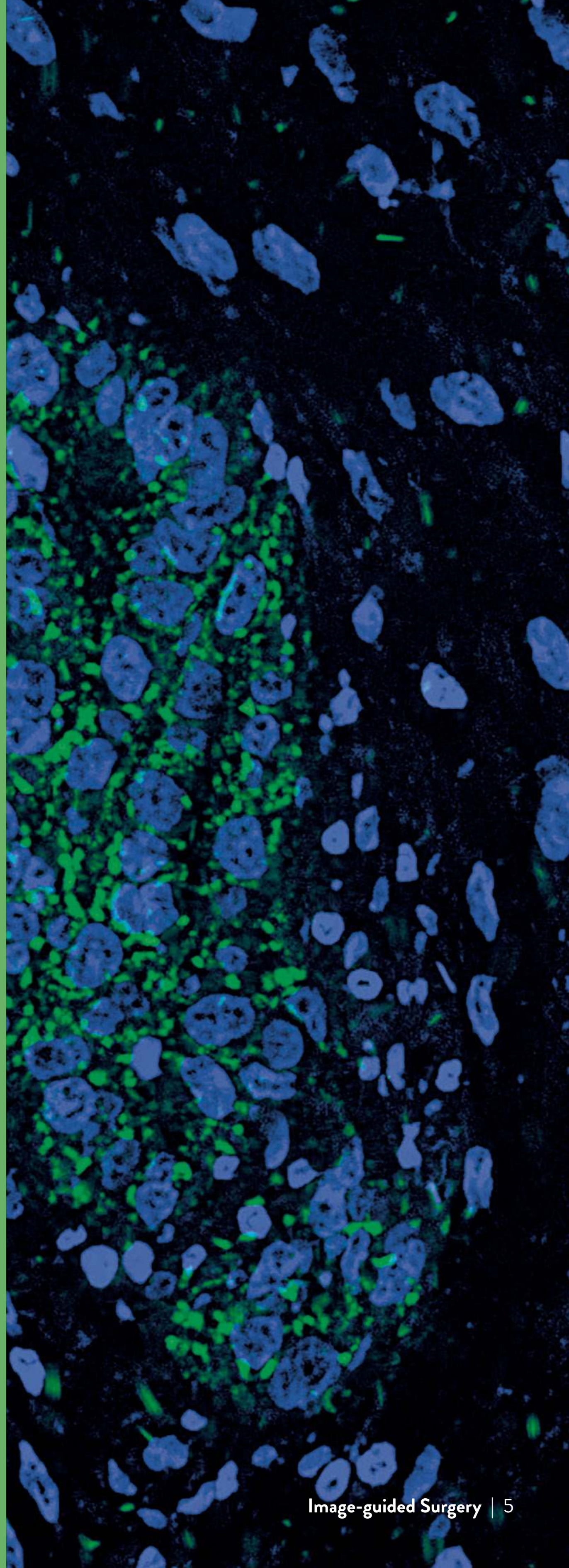
Using pharmacological measurements, CHDR can establish the optimal conditions for visualising tumour cells, metastases, and positive lymph nodes, thereby minimising false-negative signals (which would result in the incomplete removal of tumour cells) and false-positive signals (which would result in the removal of healthy tissue).

What is the optimal timing for administering and tracking the fluorescent label?

After administration, the label must reach the tumour. Initially, healthy tissue may also absorb the label, temporarily becoming fluorescent. Depending on a variety of conditions, however, the label will be cleared from healthy tissue but will remain in the tumour cells, providing a window of time during which only tumour cells are fluorescent. CHDR uses sophisticated modelling techniques to determine the ideal timing between administering the label and performing the medical procedure.

Image-guided surgery at a glance

- Image-guided surgery is a novel multidisciplinary technique that improves tumour diagnostics and increases the success of surgical cancer treatment.
- A fluorescent label is attached to a molecule (e.g. a monoclonal antibody) that binds specifically and selectively to tumour cells, making the primary tumour and metastases visible to the surgeon.
- This technique can be used in classic ‘open’ surgeries, minimally invasive surgeries, and diagnostic procedures.
- The fluorescent label itself is not pharmacologically active; however, it can be extremely useful for optimising the dosage and timing of pharmacological compounds.
- CHDR collaborates with mathematicians to develop new applications for this powerful new tool.



Fluorescent tumour markers:
a closer look

Multidisciplinary collaborations

Image-guided surgery requires the expertise of professionals from a wide range of disciplines, with researchers and physicians at the forefront. Researchers at CHDR work closely with surgeons at Leiden University Medical Centre in order to take image-guided surgery to the next level. In addition, basic researchers in the fields of oncology and immunology are developing labels that have high affinity for specific tumour types. These labels can include small molecules, antibodies, and fragments of antibodies, all of which can be engineered to emit near infrared light when activated at a specific wavelength. These applications require a solid working knowledge of chemistry and biochemistry, as well as an understanding of the properties of light and optics. Methods are also being developed to provide greater light penetration, so that deeper tumours can be detected.

The value of the pharmacological approach

CHDR approaches fluorescent labels as if they were any other pharmacological compound. First, each label is tested in healthy subjects, measuring its safety, pharmacokinetics, and pharmacodynamics profiles. Studying the relationship between pharmacokinetics and pharmacodynamics (the so-called 'PK/PD approach') can provide valuable information regarding dosage and safety, helping researchers optimise the compound's beneficial effects whilst minimising unwanted side effects.

In collaboration with surgeons at Leiden University Medical Centre, CHDR is taking a similar approach with fluorescent labels – the only difference is that these studies focus more on tissue pharmacokinetics than pharmacodynamics. In the tissue, outcome is determined largely by the ratio between desired (on-target) and undesired (off-target) fluorescence. Even in the earliest stages of development, administering increasing doses to healthy subjects can provide important information regarding key parameters, including uptake kinetics, fluorescence in surface blood vessels (e.g. in the skin, mucosa, or retina), and elimination kinetics. All of this information is then applied to mathematical models (see below), helping the researchers decide whether to proceed to the next step – giving the compound to patients. If the decision is to proceed, patient studies can start with the optimal conditions, maximising the likelihood of obtaining meaningful clinical data.

Mathematical models provide both focus and clarity

Integrating all available knowledge into a comprehensive model is essential for the success of this new field. Because animal models often have limited value in terms of clinical translation, studies in human subjects are crucial. That's why CHDR collaborates with mathematicians at Leiden University who specialise in developing robust PK/PD models. These sophisticated models can reveal which parameters are important for predicting the molecule's behaviour within the patient. Armed with this information, clinical research becomes more focused, faster, and safer. The information obtained from the mathematical model may even help researchers design better markers by 'tweaking' their biochemical properties in order to optimise both systemic and local pharmacokinetics.

A wide range of applications

Image-guided surgery is one of the latest advances in the surgical treatment of cancer and other diseases. The value of this approach is particularly evident in minimally invasive surgery, in which the surgeon operates through a small incision using a laparoscope and specialised instruments. Although laparoscopic surgery minimises tissue trauma and reduces recovery time, the surgeon cannot rely on touch to distinguish between the tumour and healthy tissue. As a result, the surgeon often must take a conservative approach, removing healthy tissue in order to maximise success and patient outcome. Using a fluorescent label can help the surgeon get back in touch.

During diagnostic procedures such as a colonoscopy, bronchoscopy, or cystoscopy, small and/or diffuse tumours often go undetected. However, if the tumour literally emits light when stimulated, even extremely small tumours will be much easier to detect, significantly improving diagnostic accuracy.

The ability to monitor blood flow is essential to many medical procedures, for example to confirm blood vessel integrity following vascular anastomosis or to measure blood flow within a tissue or organ. At CHDR, fluorescent substances are also a powerful tool for studying drugs designed to affect blood flow through even the smallest blood vessels, for example in patients with sickle cell anaemia.

The Image-guided Surgery Team

The Image-Guided Surgery (IGS) team is a unique collaboration between CHDR, Leiden University, and the Leiden University Medical Centre (LUMC). Working together, the team develops powerful image-guided approaches for use in surgery, diagnostics, and other clinical applications.

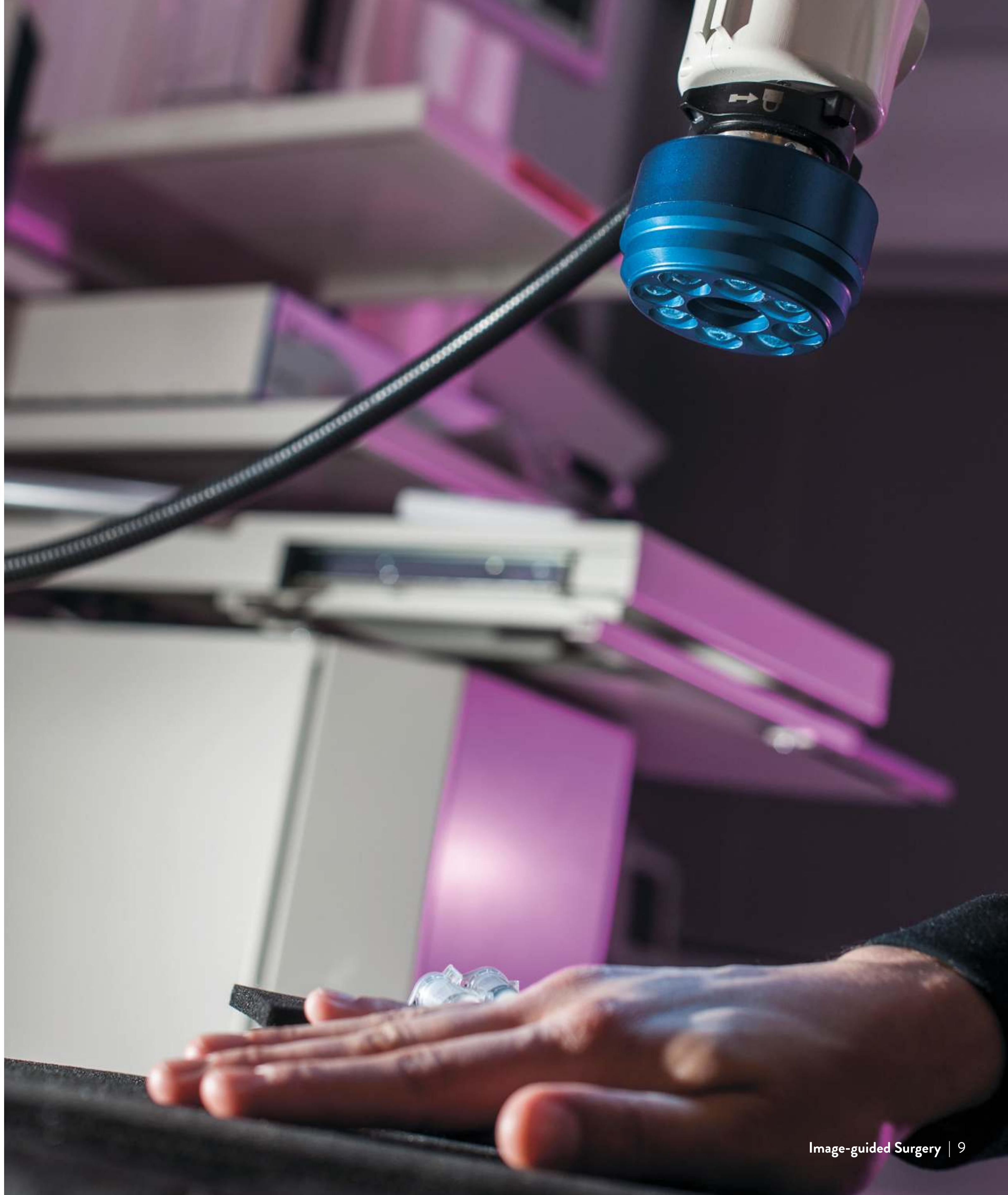
The combined effort of surgical oncologists and CHDR's world-class drug-development group opens exciting new opportunities, bringing important medical breakthroughs to the clinic.

In addition to its extensive experience with preclinical research, the group has also performed sponsored clinical studies in this emerging field, leading to several important advances, including:

- Improved outcome in both open and laparoscopic procedures;
- Development of imaging devices with a wide range of wavelengths for use in both academic and commercial applications;
- A wide variety of applications in the field of oncological surgery; and
- A comprehensive panel of tumour-targeting fluorescent probes for clinical applications.

The IGS team draws on the clinical expertise at CHDR and LUMC's surgical departments, including General Surgery, Surgical Oncology, Gynaecology, Thoracic Surgery, Urology, Neurosurgery, and Head-and-Neck Surgery. In addition, affiliations with the departments of Pathology, Radiology, Endocrinology, and Image Processing have led to advanced knowledge regarding the development and preclinical validation of fluorescent probes. The IGS team also works closely with mathematicians at Leiden University to develop PK/PD models of new and existing fluorescent probes.

Based on our vast experience with preclinical and clinical research development and our established, proven infrastructure, the IGS team is a one-stop shop for accelerated clinical translation. We offer a unique combination of expertise and research infrastructure to research groups and companies who are developing near fluorescent probes for targeting specific structures. At any point in the development trajectory we can offer our services for a fast, high quality translation from preclinical validation to human studies, ultimately improving surgical outcome and patient care.



Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

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