Navigating anatomical architecture during liver cancer treatment

Liver cancer is a leading cause of death worldwide. **Professor Samuel Kadoury** and his team are working to optimise treatment methods for both primary and secondary forms of liver cancer. Although current intra-arterial treatments have proven effective, practitioners have faced challenges in visualising the tumour target, accurately delivering the therapeutic agent into the tumour, and monitoring the impact of treatment. Using state of the art computer and imaging technologies, Prof Kadoury and his team can now construct 3D roadmaps of arterial networks and tumour tissues. These innovations will yield a new generation of intervention guidance tools, with the potential to greatly improve current liver cancer treatments.

Every year more than half a million people are diagnosed with primary liver tumours, known as hepatocellular carcinomas (HCC). In recent years, major advances have been made in developing treatments. However, their application has been hindered by technical challenges. Professor Samuel Kadoury has been working on developing novel image-guided device interventions for the arterial therapies used to treat these cancers. Based at Polytechnique Montréal & the CHUM Research Center, his team have a wealth of expertise in a broad range of disciplines, including engineering, medical imaging, radiology and physics. Together they have discovered new ways to navigate the arteries and liver tissues of patients, enabling the most accurate and effective use of existing therapies.

Most intermediate stage liver tumours are not eligible for curative treatment options. Therefore, palliative inter-arterial therapies are now the preferred therapeutic approach for patients with inoperable advanced HCC. Recently, interest has also been rekindled in extending the use of intra-arterial therapies further to treat colorectal liver metastasis. Among the most popular intra-arterial therapies used are intra-arterial chemotherapy and trans-arterial chemoembolisation (TACE) – with or without drug-eluting beads (DEB-TACE). Despite advances, the treatment approaches remain demanding and their full potential has been thwarted by technical difficulties.

DIRECT DELIVERY OF CHEMOTHERAPEUTICS

During TACE, chemotherapeutic drugs are injected into the tumour tissues. This, in turn, blocks the hepatic arteries feeding the tumour using an embolising agent (it creates a blood clot). This enhances drug delivery by inducing a static state in the arteries, thus reducing wash-out (removal) of the drug. Although TACE has proven effective against liver tumours, applying this approach has presented some major challenges. Key issues include: a lack of accuracy in targeting the optimum quantity of drug to the tumour following its release from the catheter; the risk of damage to healthy liver due to lack of specificity in embolisation; and the invasiveness of the procedure. These problems arise because, currently, much of the TACE procedure relies heavily on the clinician's experience. Decisions regarding which vessel to take to reach the tumour, the quantity of drug to inject and at what rate, when to stop, and whether it was successful, are all subjective factors.

Intra-arterial hepatic chemotherapy (IAHC) is another approach used to enhance the concentration of drugs in tumour tissue that relies heavily on pre-operative planning using MRI and CT scanning. This technique requires the precise implantation of a catheter for the repeated administration of chemotherapeutic agents. Arteries nearby that do not feed the tumour, downstream from the site of perfusion, need to be obstructed to avoid unwanted hepatic toxicity.

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ENHANCING GUIDANCE TO DECREASE TOXICITY

Fortunately, Prof Kadoury and his team are addressing the limitations of these techniques. In doing so they will help to minimise systemic toxicity from the treatments and maximise the concentration of the drug within target tumour tissues.

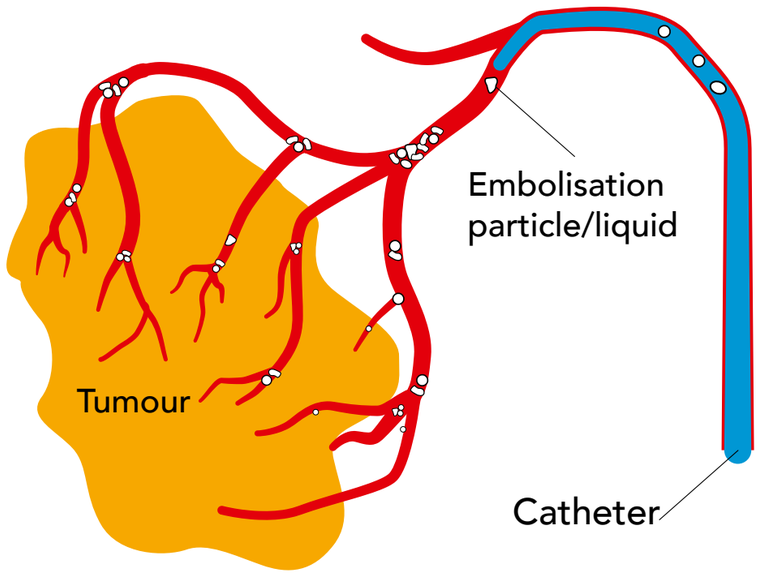
The precise delineation of tumours is essential for detecting, diagnosing and monitoring liver cancer progression, as well as informing pre-operative planning. Firstly, they have improved upon the current pre-operative systems based on magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Currently, these techniques are used to obtain datasets of the structure of the tumour and vessels, which are then segmented and reconstructed manually to give 3D models of the patient's anatomy. Manual reconstruction is not only time intensive, but also subject to human error and variation due to the qualitative nature of the image processing.

However, accurate automated segmentation has been challenging to develop due to the high degree of inhomogeneity in MRI tissue data, noise, and the variable appearance of malignant tissue. Prof Kadoury and his team have devised an automated machine learning system for metastatic liver tumour segmentation that learns the appearance of tumours in comparison to normal tissues. They validated this novel framework using a clinical database of scans from patients. Compared to other state-of-the-art methods, they found that their technique achieved the best performance.

MRA used to carry out pre-operative mapping of blood vessels has also suffered from similar pitfalls to MRI. Manual segmentation of the vessels and identification of those that feed the tumour has been incredibly challenging, greatly increasing the risk of inaccuracies. Dr Kadoury and his team have therefore designed an algorithm capable of improving the selectivity of arterial segments, which they have demonstrated has the capacity to outperform other state of the art methods, with respect to manual segmentation.

PRECISION PATH MAPPING

The researchers are now combining this pre-operative magnetic resonance-based technique with real-time MR-compatible fibre optic imaging, to intraoperatively guide the procedure. Updating current methodologies



with accurate intra-procedural imaging in real-time is of crucial importance. This is because one of the largest existing problems is that the motion from the patient's breathing and involuntary movements changes the position of the organs. This can cause deviations between the patient's anatomy and the imaged path used.

Currently, positioning of catheters and guidewires is determined through fluoroscopy. This only provides a 2D image of the catheter, making it difficult to gently and precisely guide the devices through the vessels. Dr Kadoury's research group are developing a method where preoperative 3D rotational angiography images (3DRA) of vessels are combined with intra-operative 2D fluoroscopic images of the catheter shape. This approach enables a continuous up-to-date roadmap during the procedure to improve guidance in TACE interventions.

Furthermore, they have developed a new catheter tracking technology based on optical shape sensing. Optical fibres are inserted in a double-lumen catheter and guided to the hepatic arteries, from which the 3D centreline of the catheter can be inferred with millimetre precision and updated in real-time to compensate for movement. The researchers have then integrated this new, more sensitive fluoroscopy technique with their novel pre-operative MRI 3D arterial road-mapping system.

MONITORING THE FLOW FOR 4D FINAL OUTPUT

Dr Kadoury and his research team's efforts have focused on improving treatment monitoring progress during TACE procedures, through the use of MRI-perfusion quantification and optical flow velocity (to monitor blood flow). Combined, the techniques will provide clinicians with a full 4D picture of what is happening internally during the procedure.

Following the development of these new approaches, Dr Kadoury and his team are working to fuse these into an interactive user-friendly visualisation framework harnessing augmented reality. The researchers are validating their use in both synthetic and animal models, prior to progressing to human clinical trials. If successful, they will provide a better quality of life for many patients suffering from primary and metastatic liver cancer.

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Q&A

How did you come to focus your work on improving guidance for intra-arterial liver cancer treatment specifically?

The main motivation for me was to improve the targeting of transcatheter arterial chemoembolisations, as currently only around 20–30% of the drugs that are injected in patients actually reach the tumour. There is a need to reduce the quantity of drugs that are injected intra arterially, and, to do this, improve the selectivity of the arterial branches reached by the catheter.

This can be achieved with a better 3D visualisation of the arterial network, and there needs to be real-time feedback on the catheter's location so that the tumour can be reached as closely as possible, to avoid injecting these drugs into healthy tissue. There was therefore an opportunity to develop computer software and medical devices to improve the guidance for these procedures.

What was it that interested you personally about that area?

My interest was to develop the software and engineering devices that could improve current clinical workflows in the interventional suite for liver cancer treatments. My expertise is in biomedical engineering and medical imaging; that particular problem attracted me because of the very high incidence of liver cancer and the possibility of contributing new techniques to improve life expectancy for this terrible disease. It seemed a good opportunity to simplify the physician's workload, by creating precise tools which would ultimately improve the patient's condition during therapeutic procedures.

What do you think has been the most interesting challenge you've tackled so far in the project?

It's really been the multi-disciplinary research, bringing different expertise together. As a computer engineer, I have expertise in computer software, artificial intelligence, computer vision, and image processing to help develop some of these algorithms. But the project goes far beyond computer programmes, as it requires expertise in physics and radiology, both from the engineering and the clinical side. So, the most interesting challenge has really been creating and executing this project over the past years, alongside that differing expertise.

Another challenge has been the transition from engineering to medicine: bringing these new tools and computer algorithms from the lab into the clinical workflow. Translating these experiments to *in vivo* studies requires a strong understanding of the limitations and scope of routine clinical procedures, which is quite a complex task. At the moment, we are at a midway phase; we have the tools available but there is now a need to prove their use and effectiveness in a clinical setting.

Could the new technology be applied for the treatment of other cancers or other operations?

Yes. From the diagnostic perspective, we're developing machine learning algorithms to detect cancer and model tumour heterogeneity from medical images. This could definitely be used in different pathologies such as for prostate cancer: we hope to provide a better representation of the aggressiveness of the tumour and offer a proper classification based on these machine learning algorithms.

For device navigation using optical sensing, we're also looking to other applications such as in cardiovascular imaging to treat arrhythmias, or neurovascular imaging for aneurysms. There's also some interest in the field of orthopaedics, for localising the surgeon's tool in real-time and collecting more information about tissue properties for disk replacement procedures for example.

What are the steps you still need to take to overcome the challenges that you mentioned previously, before you can apply the technology in a clinical setting?

The next step is to demonstrate their usability and accuracy in an *in vivo* setting. Right now we are preparing for animal studies, and we have in place a protocol that will evaluate these technologies on pig models. The next challenge will be how this could then be used in a clinical setting.

The project doesn't yet involve human evaluation. However, we want to have a clear picture of how this could be used in a controlled setting, first using animal models over the coming year or so, before translating the technology for human trials.

Looking a little further ahead than that, over the next five years how do you see the research progressing?

The natural progression of this research is moving past only anatomical guidance. We have reached a certain level of maturity right now in terms of spatial navigation: we are now able to locate the devices within the patient's anatomy and we are able to segment structural information from the images.

Moving forward from here though, I think what will be important is improving physiological and metabolic monitoring, and tracking (being able to estimate blood flow, temperature or sensing applied forces) and so obtaining more information related to the patient's metabolism.

In terms of diagnostic imaging, the trend right now is to develop reliable predictive models – for example, predicting the progression of cancer at a very early stage or the therapeutic outcomes. That will still be a key area of research in the next few years: to design predictive models and determine, using medical imaging, the genetic profile linked to pathology. That will help us to understand the patient's personalised characteristics, and we will be able to then associate that to an adequate cancer treatment.

Detail

RESEARCH OBJECTIVES

Dr Kadoury's research focuses on developing mechanisms capable of effectively intervening with arterial therapies in liver cancer. His current research is looking to develop and evaluate advanced interventional guidance platforms for intra-arterial procedures in liver cancer.

FUNDING

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COLLABORATORS

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BIO

Samuel Kadoury is an Associate Professor at Polytechnique Montreal and a researcher at the CHUM Research Center. He currently holds the Canada Research Chair in Medical Imaging and Assisted Interventions, and has published numerous peer-reviewed papers in leading journals and conferences in fields such as biomedical imaging, radiology and neuroimaging.

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