A New Light on Prostate Cancer

J. olde Heuvel, PhD
March 26, 2021
University of Twente

Promotor:
Prof. C.H. Slump, PhD

Co-promotors:
B.J. de Wit-van der Veen, PhD
M.P.M. Stokkel, MD PhD

The main objective of radical prostatectomy is to ensure complete prostate tumour resection while minimizing damage. Despite technical advances in surgery, irradical resection of PCa still occurs frequently. Irradical resection, better known as positive surgical margins (PSM); is defined as tumour cells present in the inked surface of the prostate on final histopathology. PSMs are associated with a higher risk of recurrence and subsequent adjuvant therapy, impacting quality of life. Diagnostic imaging of PCa has progressed dramatically over the last five years, with the introduction of specific tumour targeting tracers, such as Gallium-68 prostate specific membrane antigen ([^{68}Ga]Ga-PSMA-11). It is hypothesised that combining these tracers with a novel imaging system might assist the surgeon intraoperatively with a radical excision and thus reduce the PSM rate.
An emerging technology that might be used is Cerenkov luminescence imaging (CLI). Cerenkov radiation is induced when a charged particle travels faster than the velocity of light in that specific dielectric medium inducing polarization. As the charged particle moves through the tissue, the atoms return to their ground state, thereby emitting optical photons, also known as Cerenkov radiation. CLI images can be acquired by detecting the Cerenkov light from PET tracers using sensitive optical cameras such as electron-multiplying charge-coupled device cameras. In prostate cancer, [^{68}Ga]Ga-PSMA-11 could be used, as it can induce Cerenkov radiation and the detected rays from superficial layers might guide towards areas with high suspicion of a PSM. In this thesis, the application of PSMA-directed CLI was introduced to shine a new light on prostate cancer surgery.

First, we focussed on the requirements for accurate intraoperative margin assessment in PCa surgery. We conducted a technical performance study of CLI using ^{68}Ga in comparison to fluorine-18 (^{18}F). From this *in vitro* study we concluded that the light yield is linear to the activity concentration, in which ^{68}Ga showed a roughly 22 times higher light yield when compared to ^{18}F, while using the same activity level. Subsequently, the minimal activity concentration of ^{68}Ga which can be detected was lower, meaning that one can either image faster or inject a lower dosage of ^{68}Ga. Based on the aforementioned results an *ex vivo* clinical study using [^{68}Ga]Ga-PSMA-11 for intraoperative margin assessment was deemed feasible.

We explored whether [^{68}Ga]Ga-PSMA-11 PET/CT in patients with primary PCa can be used to obtain additional knowledge for intraoperative CLI application, with regard to the tumour location, uptake intensity and kinetics. We described a prospective study on the repeatability of [^{68}Ga]Ga-PSMA-11 PET/CT in patients with primary prostate cancer with a four-week interval between two scans. We concluded from this study that [^{68}Ga]Ga-PSMA-11 uptake on PET/CT in primary prostate cancer is repeatable. Consequently, [^{68}Ga]Ga-PSMA-11 PET/CT can be used preoperative to select patients for the main CLI study, as preoperative uptake was considered a fair indicator for intraoperative uptake.
Dynamic PET/CT scans were performed using [^{68}Ga]Ga-PSMA-11 to investigate the timing for CLI imaging. An uptake plateau was reached for the iliac artery and gluteal muscle 5 minutes post-injection (p.i.). In some patients, tumour uptake reached a plateau at 5 minutes p.i., whereas in others the uptake kept increasing over time and did not reach a plateau up to 60 minutes p.i. The hypothesis was that this difference between the uptake patterns is caused by tumour volume, in which in large tumours the uptake did not reach a plateau over time. Though not fully understood, the information might be beneficial for personalised dosing and radionuclide therapies in patient with low-volume tumour load. For the CLI study, we gained knowledge that at 5 minutes p.i. CLI imaging of the tumour is theoretically possible.

Lastly, we described the actual intraoperative use of [^{68}Ga]Ga-PSMA-11 CLI, as margin assessment technology in a prospective clinical study. The acquisition settings of the technique were optimized for the intraoperative *ex vivo* setting. CLI was able to accurately detect tumour in cleaved prostate specimens. In addition, the PSMs on the prostate surface were correctly identified on CLI. With respect to the safety aspects of CLI, the radiation exposure to staff was within acceptable limits. The scrub nurse next to the patient was exposed to the highest dose (0.016 mSv per procedure). The exposure to other staff was at least 3 times lower.

We elaborated on the accuracy of CLI compared to histopathology and characterised the novel identified bioluminescence signal. Solely looking at the presence of a hotspot on CLI (yes/no), the agreement between CLI and histopathology was only 31%.

Disagreement occurred profoundly at the base. When applying visual image interpretation, by giving hotspots a Likert score, the agreement improved to 59%. When close margins on histopathology (tumour ≤1mm from the inked surface) were also included as positive, the agreement was 82%. The remaining mismatch between CLI and histopathology was likely caused by the use of diathermy during surgery. Diathermy induced a bioluminescence that hampered the visualisation of the PSMs.

In conclusion, this thesis describes the possible value of CLI during prostate cancer surgery and shows that it has potential in highlighting areas at risk of PSMs. CLI might have profound clinical impact in other types of oncological surgery, taking in consideration a proper tumour to background ratio, depth sensitivity within the range of the PSM definition and the ability for intraoperative use.

The choice of radiopharmaceutical influences the CLI accuracy, regarding the penetration depth and signal yield. Next, the injected activity should be within an acceptable range regarding radiation exposure to patients and the clinical team. Finally, preoperative imaging gives essential information involving lesion uptake and location. As with every new complicated medical technology, implementation depends on teamwork and comes with hurdles. After a learning curve, CLI might light the path to better, more precise cancer treatment.

judith4192@gmail.com ♦

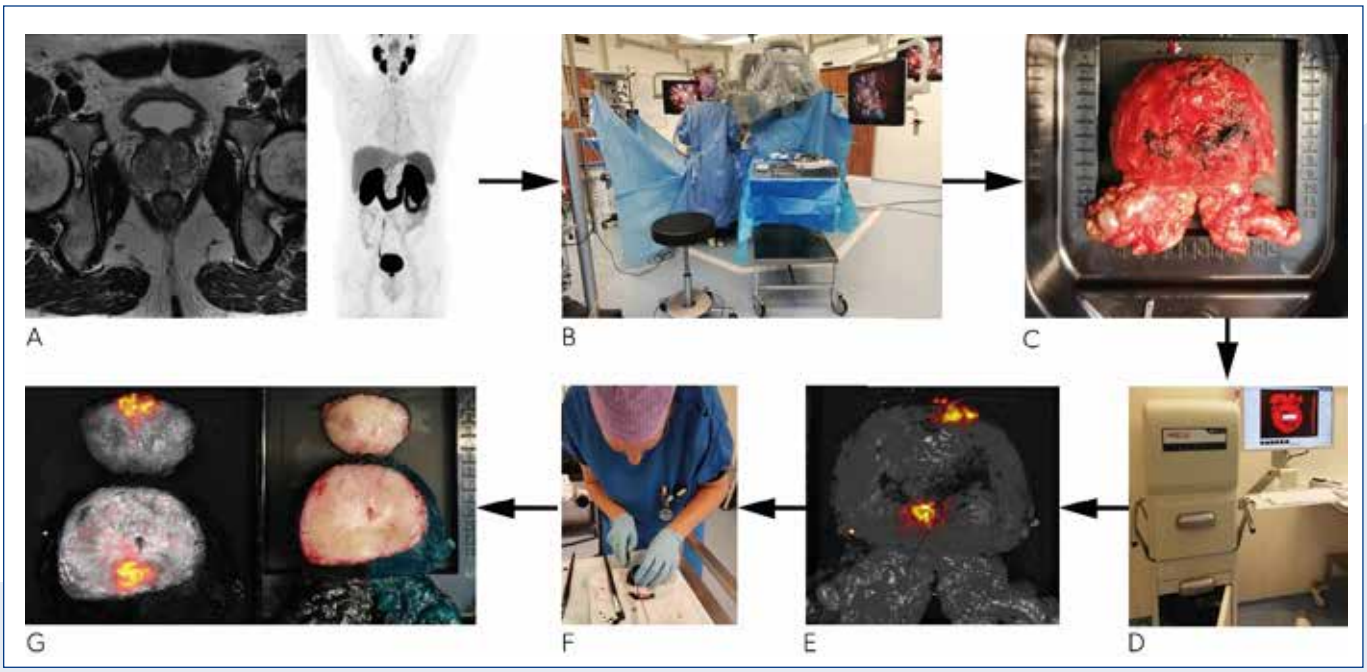

Figure 1. Workflow of the current CLI study, (A) A pre-operative MRI scan and [^{68}Ga]Ga-PSMA-11 PET-CT. (B) During surgery [^{68}Ga]Ga-PSMA-11 is administered i.v. (C) The prostate is positioned in a disposable specimen tray. (D) Images of all six sides of the prostate using the CLI device. (E) Unfiltered Cerenkov image of the prostate specimen (F) The prostate is inked and cleaved ~1cm from the apex (G) Image of the cleaved prostate and the corresponding CLI image.