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Cerenkov Luminescence Imaging for surgical margins in radical prostatectomy: a surgical perspective

RE: Invited Perspective for Intraoperative 68Gallium-PSMA Cerenkov Luminescence Imaging for surgical margins in radical prostatectomy - a feasibility study

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Background:

"How can I reduce my positive surgical margin rate"? This is a common refrain from the urologist performing radical prostatectomy (RP) for localised prostate cancer. The avoidance of positive surgical margins (PSMs) during RP is important to reduce the likelihood of biochemical recurrence and the subsequent increased risk of metastases and death from prostate cancer(1). PSMs increase the likelihood of receiving additional treatment such as pelvic radiotherapy by up to five-fold(2), as well as increasing the likelihood of local morbidity and the financial burden of additional treatment. Despite advancements in surgical technologies, a 2017 meta-analysis found that rates of PSMs for open RP was 31.4% (range 21–53%), while the rate of PSMs for robotic-assisted RP was similar at 31.7% (range 14–50%)(3).

Currently, options for surgeons to prevent PSMs are limited and include pre-operative and intraoperative strategies. Regarding the former, traditional risk stratification is based on characteristics such as digital rectal examination, multiparametric magnetic resonance imaging (mpMRI), biopsy findings, and, more recently, PSMA PET/CT(4). However, these studies are often performed many months prior to surgery and the true pathology can advance in the interval. Intraoperative techniques such as fresh-frozen sections (FFS) may be taken for intra-operative assessment, however there remain concerns about high rates of false-negatives(5). Recently, FFS has been incorporated into the NeuroSAFE principle aimed at improving functional outcomes by facilitating preservation of neurovascular bundles in cases of uncertain tumour breach into these regions(6). However, we await level 1 evidence to support worldwide use of this method, and pathology resource and expertise limitations will persist regardless of the data supporting FFS to reduce margins. Therefore, additional strategies to reduce PSM rates are welcome.

PSMA-based technologies in prostate cancer:

^{68}Ga PSMA-PET is a powerful imaging modality in PC diagnosis and treatment planning. It relies upon antibodies or small molecules to target a particular protein found in prostate cells known as prostate specific membrane antigen (PSMA). Because PSMA is expressed in greater concentrations in PC cells it has enabled it to be targeted through PET-imaging. To enable imaging, the molecules that target PSMA are radiolabelled, often with ^{18}F or ^{68}Ga, and once they have accumulated in PSMA-avid tissue their emissions can be captured by PET camera. This has led significant advances in the detection of local and metastatic PC in both its primary and biochemically recurrent disease stages(7). Furthermore, novel applications of PSMA technology are now beginning to emerge and offer to transform intra-operative evaluation of surgical margins in RP(8).

Cerenkov Luminescence Imaging (CLI) is a technique that was discovered in 2009 and involves the detection of Cerenkov photons(9). Conveniently, these photons are emitted by the same radiolabelled molecules used in PSMA-PET (^{18}F and ^{68}Ga), and are optically captured and emitted at the same time as the annihilation photons

traditionally detected by the PET camera. These images are then overlaid to provide a visual assessment tool of margin status of the tumour specimen(8, 10). Although CLI provides only lower-resolution 2D images, not high-resolution 3D images when compared with PET, it is comparable with requirements for image-guided surgery(10). Novel advances have enabled increased portability of CLI-systems giving surgeons real-time, intraoperative CLI based evaluation of surgical margins in tumour resection(10).

Article in focus:

This single centre prospective study by Darr et al(11) evaluated the feasibility and accuracy of intraoperative ^{68}Ga-PSMA CLI to assess surgical margins in RP. Conducted over 17 months between 2018-19, 10 men with high-risk PC undergoing RP with no prior history of prostate surgery, known distant metastases, or contraindications to surgery, were included in the study. Initially ^{68}Ga PSMA-PET scans were performed on subjects 45-60min after having received intravenous injection with dose-adjusted ^{68}Ga PSMA-11. Following confirmation by experienced nuclear medicine physicians of no distant metastases, subjects immediately proceeded to RP with extended pelvic lymph node dissection. This was performed by two surgeons to minimise operative time and subsequent radiotracer decay. Following removal of the excised prostate, the specimens were placed into the LightPath© imaging chamber in the operating room to enable CLI. Images were acquired within 300 seconds (a significant improvement on the time taken to retrieve a FFS result). Regardless of the CLI results, the surgical course remained unaffected and no further tissue was resected even if CLI results suggested positive margins. The median time for the subjects between injection of IV injection and start of surgery was 223 minutes (range: 153 minutes to 328 minutes), whilst the time between IV injection and CLI image acquisition was 333 minutes (range: 282 minutes to 429 minutes). Three of the ten subjects had PSMs, which is consistent with standard rates of PSMs at RP(1). Two of the three (66%) PSMs had been identified by intraoperative CLI and the grade of cancer identified at the positive margins was International Society of Uropathology (ISUP) grade group 4 and 5 with diameters of 2mm and 4mm respectively. The PSM that was not identified by intra-operative CLI consisted of ISUP grade group 3 PC supporting pre-existing data that has demonstrated reduced PSMA expression on lower-grade PC(12). Finally, only 25 of the 35 regions of interest (ROI) on CLI were found to actually demonstrate positive margins by standard histopathology, giving a 28% false-positive rate. As the majority of the false positives were seen at the prostate base, Darr et al. suggested ^{68}Ga-containing urine (renally excreted) contamination as a potential explanation for the false positives. However, it was also noted that the false positives had PC tissue deep to overlying benign prostatic tissue, suggesting an intrinsic issue with the photon range of the radiotracer rather than urine contamination.

Discussion:

Recent advances in nuclear imaging have enabled the development of relatively cost-effective and portable devices to provide intraoperative guidance of surgical margins. Whilst only in early stages of integration into clinical practice, intra-operative CLI offers the possibility to give surgeons real-time evaluation of surgical margins in cancer surgery. The device used in the study features a light-tight imaging chamber where the resected tumour specimen is placed. The specimen is then captured by both CLI-acquisition imaging and standard white-light imaging. By combining these images, PSMs are able to be seen on tumour specimens allowing for immediate further surgical resection if required. Of course, a decision to resect more tissue is a significant one, and the current false-positive rate of 28% reported with CLI in this study means that surgeons are unlikely to further resect based on current data. CLI has been previously described in neurosurgery and breast conserving surgery(10), and this study is the first of its kind to evaluate CLI during RP for PC.

Whilst this study was low powered and only designed to demonstrate feasibility of intraoperative CLI to reduce PSMs, some interesting observations could be made, and the authors are to be congratulated for this novel work. First, the only PSM missed by CLI contained ISUP grade group 3 PC at the surgical margin. Whilst this is consistent with other studies showing reduced PSMA expression in lower grade PC(12), the interval time between PSMA-agent injection and CLI (median 333 minutes) was long and potentially detrimental to identification of lower-grade PC. Future studies may aim to reduce the interval time between PSMA-agent injection and commencement of surgery to improve signal intensity and potentially overall sensitivity of CLI. Second, a high number of the false positives were noted at the base of prostate. The authors speculate that the presence of radioactive tracer in the urinary bladder (ie close to the base of prostate), might have explained this. As such, rinsing the prostate specimen with saline prior to performing CLI was recommended in future studies. Third, the false-positive surgical margin was found to have PC tissue deep to the surgical margin with overlying benign tissue. The authors suggest that using ^{18}F as the radiotracer instead of ^{68}Ga may reduce false positive as it has a reduced mean positron range in tissue (0.54 vs. 2.83mm) preventing deeper PC tissue emitting false-positives signals at benign surgical margins. Nonetheless, even with such proposed improvements, there will always be a potential for CLI signal to identify cancer very close to the edge of the specimen, which may not translate into a PSM on histopathology. These will always be considered a “false positive” if there is no PSM on histopathology, although there may not be clinical significance. Lastly, like any new technology, there will be a learning curve for surgeons and operating room staff, and a need for nuclear medicine physicians, urologists, and pathologists to develop relationships and pathways(13). Part of the challenge will be to overcome any concerns and logistical barriers to the handling of radioactivity in new clinical environments such as the prostate cancer operating room.

Of note, a further very recent study of six men undergoing RP and CLI using the same LightPath© system, the authors reported that CLI correctly identified negative and positive surgical margins in three of five patients(14). One patient was excluded due to unsuccessful labelling on the day of surgery.

In conclusion, whilst Darr et al present a promising technique for intra-operative assessment of surgical margins in RP within a small sample of patients, this needs to be further explored in a larger study with a more clearly defined CLI protocol (currently being undertaken). Furthermore, studies looking at using ^{18}F rather than ^{68}Ga may be useful to investigate its impact in reducing false-positives in intraoperative CLI.

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