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Recent Progress of Cerenkov Luminescence Imaging

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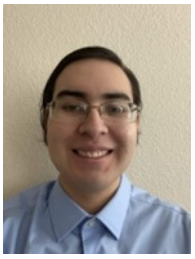

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Cerenkov radiation is produced when a charged particle moves faster than the speed of light in media. At a well-defined angle with respect to the particle's trajectory, the particle induces coherent electromagnetic radiation with a continuous spectrum. This radiation then propagates in the media and is detectable at a large distance. The constructive interference of the coherent radiation results in a number of Cerenkov radiation photons that are proportional to the distance traveled by the charged particle and inversely proportional to the square of wavelength.[1] Thus most Cerenkov radiation photons are in the blue region.

In 2009, Robertson et al. have, for the first time, shown that the visible photons from Cerenkov radiation in small animals are detectable with a laboratory camera.[2] These observations were further validated by many laboratories and resulted in a new hybrid imaging modality named Cerenkov Luminescence Imaging (CLI) which has two major advantages.[3–5] One is that CLI provides a low cost alternative to nuclear medicine imaging like positron emission tomography (PET) by low cost optical scanners such as PerkinElmer Caliper IVIS 100.2,[6] The other is direct imaging of β^--emitting radionuclides such as ^{90}Y.[6] Since the emergence of CLI, many scholars have reported different applications such as reporter gene expression imaging,[7] $\alpha_v\beta_6$ integrin tumor imaging [8], and pH values detection.[9] All these applications have demonstrated the popularity and significance of CLI.

Recently, the applications of CLI have expanded into time of flight (TOF) PET detector due to its extremely small or negligible rising and decaying time.[10] We will review this exciting progress later.

The major weakness of CLI is its low photon number which is easily overwhelmed by ambient lights. A small LED light generates much more optical photons than the Cerenkov luminescence photons from any in vivo CLI studies. However, this weakness can be overcome by using the high energy external X-ray beam in radiotherapy. The high energy secondary electrons ionized by the X-ray beam generate a high number of Cerenkov photons to be measured for radiation dose monitoring and tissue oxygenation sensing.[11,12] Furthermore, the high number of Cerenkov photons in radiotherapy can be used as the excitation source for FDA-approved photosensitizers of photodynamic therapy (PDT), which could be used to enhance the radiotherapy.[13]

Another weakness of CLI is short wavelengths in the blue region. Thus, most Cerenkov photons are absorbed before they reach the body surface for measurement acquisition. One way to overcome this weakness is to use an endoscopic system to detect the emitted Cerenkov photons closer to targets.[14,15] Another way is to shift the wavelengths by embedding nanoparticles or quantum dots into the subject.[16,17] However, due to the toxicity concerns of the nanoparticles and quantum dots, most applications of this approach are only for preclinical imaging.

In the following sections of this letter, we will review the aforementioned topics and their recent research progress.

Cerenkov Luminescence Tomography

CLI is a two-dimensional (2D) imaging modality and its applications are limited by photon intensity uncertainty which depends on the target depth. If CLI would like to be an alternative imaging approach of PET, three dimensional CLI is highly desired. In early

2010, Li et al. demonstrated for the first time a new imaging method called Cerenkov Luminescence Tomography (CLT), in which the biodistribution of nuclear radioactivity inside a small animal is traced back from the surface measurements of optical photon intensity from Cerenkov radiation with an inverse algorithm.[18] Later, using a similar approach, Hu et al. also validated CLT's feasibility with SPECT imaging.[19]

Recently, CLT has been investigated with many novel reconstruction approaches such as stacked denoising autoencoder, multilayer fully connected neural network, non-negative iterative convex refinement, and total variation constrained graph manifold learning strategy. However, the qualities of reported CLT images are not good enough to make CLT an acceptable modality in research labs due to the following reasons. Firstly, the reconstructed CLT targets are very sparse, which is not always the case for preclinical models. Secondly, the spatial resolution of CLT is still limited by very strong optical scattering, which is difficult to be overcome with reconstruction methods. Lastly, CLT reconstruction is based on finite element mesh for solving the diffusion equation. It is not trivial to construct the finite element mesh automatically.

Endoscopic CLI

CLI is a kind of optical imaging in which the emitted optical photons are strongly scattered and most photons are absorbed in tissues before they propagate to body surface for measurements. Thus, a catheter based endoscopic CLI is one way to overcome the limitations of imaging depth to reach the deep organs or tissues directly. In 2012, Liu et al. proposed this idea and demonstrated its feasibility with both phantom and mice imaging [14,15]. The same group has also shown that the beta emitting radiotracers like ^{90}Y could be imaged by Cerenkov luminescence endoscopy with much better sensitivity compared with the gamma emitter radiotracer ^{18}F. In 2014, Cao et al. built a CLI endoscopic system and evaluated its performance with phantom and pseudotumor studies.[20] This approach was first applied to human subjects by Hu et al., in which they performed a pilot clinical study in imaging the cancer after administration of FDG. Their study was cross validated with CT-PET imaging [21]. Recently, the performance of an endoscopic CLI system was optimized and indicated that the system can detect radioactivity as low as 0.83 μCi with an imaging time of 1 minute for the radiotracer of ^{68}Ga, which is very impressive.

Intraoperative surgery guidance

Like PET and SPECT, CLI can be used to guide surgeons during a tumor resection. In 2011, Holland et al. deployed CLI with a Zirconium radiotracer and compared images across two cancer types. This study showed that it was possible to track expression of prostate specific membrane antigen (PSMA) in prostate cancer grafts, as well as breast cancer positive tumors BT-474. They compared their CLI images with PET images of the same samples.[22] Soon after it was demonstrated that the CLI of ^{18}F-FDG radiotracer could also provide a suitable method for imaging the internal structure of lymph nodes.

During intraoperative surgery, it is critical that there is a method to determine the cancer margin. Efforts have been made to improve the accuracy of CLI to avoid patients from developing metastases in the future. The blood vessels in tumors was successfully visualized in CLI images with the use of negative contrast.

Recently, with the light proof chamber and the CLI fiberscopic device, Pratt et al. showed that the fiberscopic CLI could serve as a method for superficial disease surveillance and provided a unifying molecular imaging method for nearly all radionuclides currently used in clinic.[23] Figure 1 shows a schematic of the imaging system, in which the patient is in a dark, light-tight chamber and the Cerenkov photons on the patient's body surface are acquired by a sensitive fiberscopic based camera.

Therapy Monitoring and Enhancement

Immunotherapy: Immunotherapy employs therapeutic drugs to activate the immune system to fight malignant diseases. The applications of CLI also extend to the monitoring of these specialized drugs. In 2012, Xu et al. investigated this application to the immunotherapy treatment of lung and prostate cancer. Using mouse models, they investigated the signal of commonly used radiotracers from treatment and control groups.[24] They concluded PET and CLI results correlated very well, suggesting that CLI can be used as a method for cancer drug monitoring. Additionally, CLI has been implemented as a method to track diseases such as lymphoma which

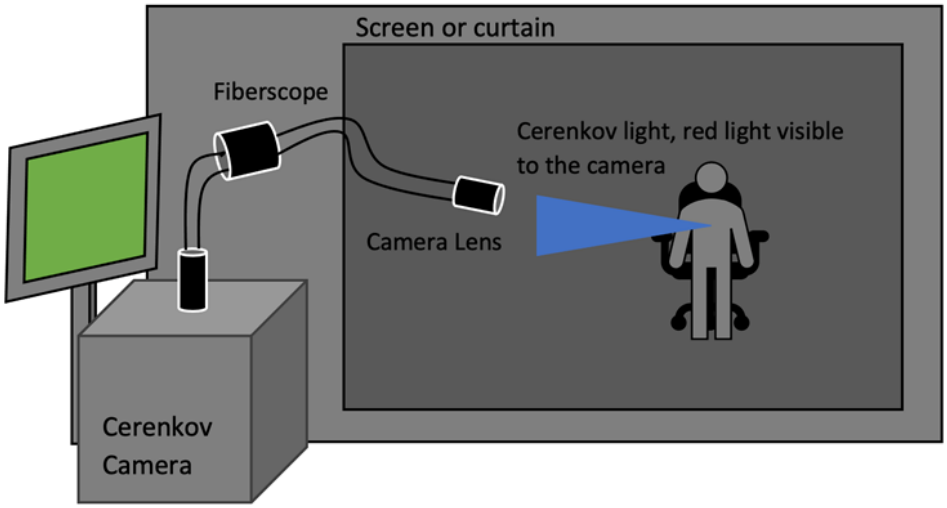

Figure 1 A schematic of a clinical Cerenkov setup using a fiberscope with a dark enclosure to prevent outside light from interfering with patient imaging.

affects the B cells in the model organism. This was done on transgenic mice containing human protein CD20 in the cell membrane of B cells. A Zirconium radiotracer, paired to a biomolecule that tracked the presence of the CD20 membrane protein, was used for generating CLI signals which indicates the expression of CD20. Significant agreement between CLI and PET suggesting was found, which indicates that CLI can be used as an alternative to monitor immunotherapy. The concept of Cerenkov radiation based photoimmunotherapy was reported and its efficacy was compared with near-infrared (NIR) photoimmunotherapy on breast cancer cells. While the Cerenkov radiation photoimmunotherapy was successful in suppressing the tumor size, it was less effective than the NIR photoimmunotherapy with some inconsistencies in producing bioluminescence.

Chemotherapy: Patients with cancers require constant monitoring for their chemotherapeutic treatments. CLI can be used to track the chemotherapeutic treatments of such patients.[25] Such efforts have been made, although the study was applied to small animal models only. In this study, Hu et al. were able to use CLI to quantify tumor uptake of ^{131}I-NGR in tumor bearing mice. This allowed them to get a quantitative measurement of the tumor activity since ^{131}I-NGR was bound to CD13 in a soft tissue cancer, HT1080. However, they did note that CLI has limited penetration depth.

Photodynamic Therapy: The activation of photosensitizer molecules is necessary for photodynamic therapy, and the use of a Cerenkov radiation radiotracer as a light source for this process has been investigated. It has been demonstrated that in cells and mice the 18F-fluorodeoxyglucose (^{18}F-FDG) could cause uncaging of the drugs from the Cerenkov luminescence for the treatment to the tumor. Because optical photons at NIR region have larger penetration depth than the photons at blue color, the wavelength shifting of Cerenkov luminescence from blue color toward NIR region has been explored for better PDT efficacy. The main advantage of Cerenkov radiation excited PDT is that the radiotracers can target deep cancer directly so that there is no depth limitation of light penetration. The limitation of this approach is the small photon number emitted per decay. Thus, Cerenkov radiation induced PDT may be a supplemental therapy along with other cancer therapy.

Emerging Applications of CLI

Time of flight measurement in PET detector

The Cerenkov photons are generated promptly in crystals or transparent semiconductors when a 511 keV gamma ray interacts with it. These promptly generated Cerenkov photons could be used to obtain the high TOF resolution in PET imaging. This idea was first demonstrated by Sun II Kwon et al. in 2016, in which they achieved the coincidence resolving time of 560 picoseconds (ps) using a pair of 3x3x20 mm^3 BGO crystals [10]. The same group also demonstrated this application using Thallium bromide (TlBr) detectors with a coincidence time reso-

lution of 330 ps. It is very impressive that Ota et al. developed a Cherenkov-radiator-integrated microchannel plate photomultiplier tube, with which they achieved a coincidence time resolution of 30.1 ps [26].

Radiation dose estimation and quality assurance

The emitted Cerenkov radiation from the object surface due to external beam radiotherapy can serve as a real time metric for absorbed dose. Current external beam radiotherapy treatments use MV electronic portal imaging (EPID) to monitor the radiation beam that passes the patient. However, the EPID does not provide good soft tissue contrast and the anatomical reference points for treatment verification and safe repeatability are limited to patient bone structures or implanted fiducial markers. Other methods exist which employ film, ionization chambers, TLDs, etc. which require additional time for processing and suffer from small FOV.

Cerenkov superficial dose monitoring concept through Monte Carlo simulations was studied, in which flat and cylindrical phantoms were irradiated with megavoltage (MV) X-ray beams and it was found the Cerenkov emission was proportional to the dose. Later, Jarvis et al. clinically demonstrated the use of Cerenkov emission as a method to visualize real time surface dose from breasts with radiation treatment by MV X-ray beams.[27]

To overcome limitations with patient specific breast tissue optical absorption and scattering properties, the tissue properties acquired from CT imaging was used to compensate for the tissue property limitations by adding a correction factor in the Cherenkov luminescence image. Cerenkov emission as a quality assurance tool in electron radiotherapy was also explored. The Cerenkov emission from a water phantom excited by electron beams was recorded with a standard commercial camera. After comparison of dose measurements from ionization chamber measurements, it was found that the Cerenkov method was linear with dose and independent of dose rate.

The Cerenkov radiation arising from the nuclear decay of therapeutic radionuclides can serve as a radiation dose monitoring tool. It was reported that the Cerenkov emissions induced by a therapeutic administration of 131-Iodide was used to monitor the dose distribution of the drug in the patient thyroid. The application of Cerenkov luminescence imaging to monitor the radiation dose from ^{90}Y-labeled gastrin releasing-peptide receptor in nude mice models was also explored.

External beam radiotherapy monitoring using CLI

External beam radiotherapy employs fast charged particles or high energy X-ray beams to treat deep malignant tissues in the patient. As a result, Cerenkov radiation emission occurs if the charged particles (or ionized charged particles) travel faster than the Cerenkov threshold in tissues. As an example of the phenomena, Axelsson et al. reported that a fluorophore, protoprphyrin IX, embedded in a biological phantom, can be excited by the Cerenkov radiation photons generated with external high energy X-ray beams.[11] Axelsson et al also assessed tissue oxygenation in phantoms and mice in real time with CLI induced by external beams as a method to monitor the efficacy of the radiation therapy.[12]

Unlike other external beam therapy, proton therapy deposits most of the radiation dose at the end of their path and subsequently exhibit a high dose gradient fall off known as the Bragg Peak. The proton stopping powers estimated from CT images result in millimeter uncertainties of the proton range. Yamamoto et al. explored CLI as a range estimation method during proton therapy in water phantoms.[28]

Radiotherapy enhancement with Cerenkov luminescence induced PDT:

As reported before, there are plenty of Cerenkov photons emitting from radiotherapy using high energy external X-ray photons. Thus, it is possible to use these emitted Cerenkov photons to excite photosensitizers for PDT. With the cultured cancer cell models, Guo et. al. demonstrate the efficacy of the Cerenkov radiation induced PDT.[13] Considering the fact that there are many clinically available PDT photosensitizers and plenty of Cerenkov photons near the tumor, the PDT enhanced radiotherapy might be worth more studies in the future.

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