Journal of Research High School

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

Recent Advancements of Cherenkov Radiation for Cancer Imaging and Treatment

Andrew Lee[1] *

[1]Avon Old Farms School, Avon, CT, USA
*Corresponding Author: joonseoandrewlee@gmail.com

Advisor: Federico Nova, federico.nova@stfc.ac.uk

Received January 17, 2023; Revised August 23, 2023; Accepted, September 25, 2023

Abstract

Since successful bioimaging in 2009, many studies have explored Cherenkov Radiation's potential value in medical diagnostics and treatment. By highlighting major accomplishments to date, this review proposes that Cherenkov Radiation has strong potential to become a novel class of modality in cancer molecular imaging. The basic principles of Cherenkov Radiation are explained. Variable conditions such as threshold energy and refractive index of tissues are described in the context of cancer diagnostics. Cherenkov luminescence imaging and tomography are outlined, as well as the milestone clinical trials with respective strengths and weaknesses. Application of Cherenkov in radiation dosimetry is discussed. Current research in Cherenkov photodynamic therapy is introduced, with many studies implying better penetrance than conventional therapy. Finally, current limitations of Cherenkov Radiation, especially its inability to reach deeper anatomical structures are examined. Despite significant challenges to overcome, applications of Cherenkov Radiation are gaining momentum in the field of oncology.

Keywords: Identity, Gender, Socioeconomic class, Education, Politics

1. Introduction

Fundamentally, molecular imaging allows for visualization of the biochemical processes of an active cell, without disturbance of the target cell and its environment (Rowe & Pomper, 2022). Molecular imaging is especially useful for cancer diagnostics and treatment monitoring, as cancer cells behave very differently compared to normal cells in metabolism. Cancer cells are characterized by their ability to rapidly grow and divide. In order undergo uncontrolled proliferation, cancer cells must consume additional nutrients to meet the increased energy demands (Chen et al., 2007). Molecular imaging utilizes the abnormal metabolic rates by using tracers that participate in the metabolic processes. Tracers may be radiolabeled or have other intrinsic properties that can be detected (Rowe & Pomper, 2022). Once a tracer is thought to be taken within the cell, a sensor or a scanner can detect the tracer and translate the detection into spatial representations such as images or graphs. The most ideal molecular imaging will have a high-affinity tracer that follows metabolic process unique to cancer, that can be detected by a scanner with high sensitivity, and high spatial, contrast and temporal resolutions. In addition, the imaging must be affordable to allow continuous, repetitive use for each patient. The current molecular imaging modalities used in oncology are limited in variability. Clinically, the most common are Magnetic Resonance Spectroscopy (MRS) and radionuclide modalities such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Although widely available, with low sensitivity and limited metabolites, MRS is used mostly for brain and prostate cancers in clinical settings (Hernot et al., 2019). SPECT is also widely available but is challenged by low resolution and low sensitivity (Wilson et al., 2020). PET is highly sensitive, and carries potential for high specificity, with more tracers being developed (Jadvar, 2016). However, its current high cost prevents widespread use. Therefore, improving current modalities and

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

developing new imaging methods are necessary to advance the field of oncology.

Cherenkov radiation (CR) is a form of light emission that occurs when a charged particle exceeds the local speed of light in a dielectric medium. CR biomedical imaging was first successful in 2009, and many innovative studies produced high quality animal and human tissue imaging (Robertson et al., 2009). CR's unique broadband emission spectrum, spectral weight in the ultraviolet and blue wavebands, and local generation of light within a given tissue, have made it an attractive new modality in cancer imaging and treatment. This review will first introduce the general concept of CR, and then highlight the major milestones of CR applications in the field of oncology. Most articles were chosen from keywords "Cherenkov Radiation", "oncology", "Cherenkov luminescence imaging" searches in Pubmed and OVID databases. Others were excavated from articles found from the databases. All articles were accessed for credibility and were peer reviewed. By summarizing the notable accomplishments from 2009 to date, the authors intend to demonstrate that CR has the full potential to become significant and permanent class of modality in molecular imaging for oncology.

2. Cherenkov Radiation Theory and Required Conditions

In 1988, Oliver Heaviside predicted that a point charge would produce a conical wavefront whenever it was to travel at a speed greater than the speed of light in a medium as shown in Figure 1 (Ciarrocchi & Belcari, 2017; Das & Boruah, 2022). This theory later explained the 1934 phenomenon when Cherenkov observed a blue glow surrounding a radium salt solution.

Light can be slowed by the medium it passes, and its speed may be significantly less than speed of light in vacuum, c = 299,792,458 m/s. For example, the speed of light in water compared to in vacuum is reduced by 25%. Cherenkov radiation occurs when a charged particle passes through a polarizable dielectric medium with a speed greater than light's speed in that medium. As the charged particle travels, it rapidly polarizes the nearby molecules, aligning them in a polarizing field. As these polarized molecules return to their ground state, they emit light photons, observed as luminescence radiation. The emitted light will travel as a wavefront in the direction at an angle θ from the direction of particle travel, shown in Figure 1.

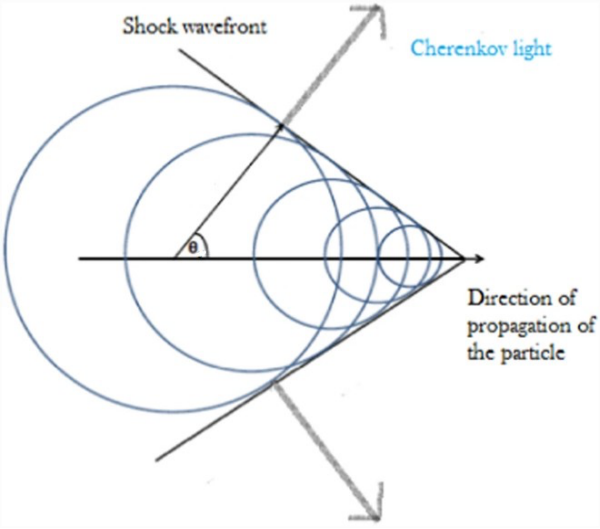

Figure 1. Cherenkov radiation is generated at an angle to the direction of the travelling particle, defined as θ, which is related to the energy of the particle. The diagram taken from (Das & Boruah, 2022) and adapted by the authors of this study.

The kinetic energy of the particles must exceed certain thresholds to produce CR. The required threshold energy can be obtained through the following equation, where m is the mass of the particle, c is the speed of light, and n is the refractive index (Tanha et al., 2015):

$$E_{min} = mc^2\left(\frac{1}{\sqrt{1-\frac{1}{n^2}}} - 1\right)$$

In addition, the intensity of Cherenkov radiation is related to the velocity and kinetic energy of the particles and the r efractive index of the environment. Figure 2 shows the inverse relationship between the energy threshold and the index of refraction. It is known through experimental trials that most biological tissues require at least 219 keV of energy when assuming a refractive index of 1.4.

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

The intensity of produced photons increases with the refractive index. Since different tissues have different refractive indices as shown in Figure 3, it is possible to observe different intensities of CR and differentiate between healthy and tumor tissues.

The charged particles originate from radioisotopes with unstable atoms which decay in order to achieve stability. During this decay there is a release of radiation in the form of energy and a particle: alpha (α), beta (β) or gamma (γ). Although theoretically all charged particles can produce CR as long as they exceed the threshold, radioisotopes that can produce useful CR in biomedicine are limited to beta emitters (Mc Larney et al., 2021). Gamma particles cannot produce CR due to low energy of secondary electrons from Compton scattering and tissue interference. Additionally, alpha particles used in medicine cannot exceed the energy threshold required to produce CR. Fortunately, many beta emitter radionuclides currently used in the industry contain greater energy than threshold, and thus can produce Cherenkov photons in water and tissue.

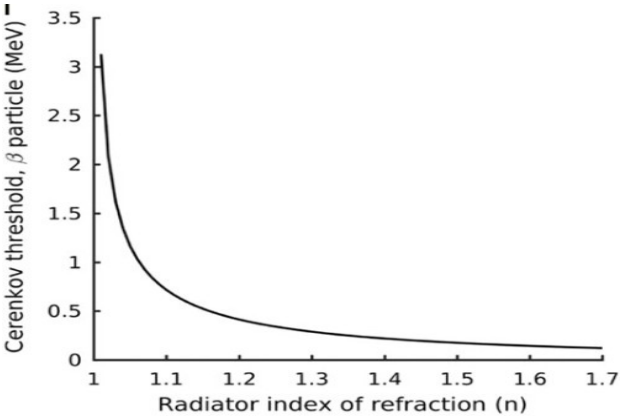

Figure 2. Cherenkov energy threshold for β particles to produce CR vs the refractive index of the environment. This graph assumes a β particle with a kinetic energy of 0.511 MeV (McLarney et al., 2021).

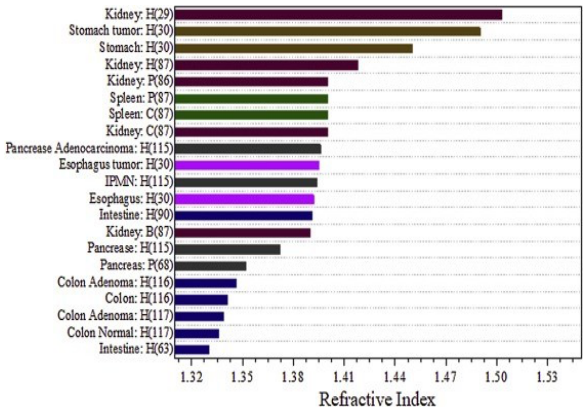

Figure 3. Refractive index values for miscellaneous tissues, including cartilage, heart, lungs, thyroid, breast, and neck. Note differences between malignant and benign breast, thyroid tissues (Khan et al., 2021).

In addition, high energy x-rays emitted by linear accelerators (LINACs) are also able to produce CR (Bianfei et al., 2022). This is relevant as LINACs are commonly used during clinical radiotherapy. During the external beam radiation therapy (EBRT), Compton scattering occurs where x-ray photons transfer energy to electrons, causing some to be ejected from their orbitals. If the ejected electron travels faster than the velocity of light in the tissue, CR will be generated (Axelsson et al., 2011). This property gave the potential for Cherenkov to be used to monitor EBRT in real time. Similarly, high-energy electron beams, heavy ion and proton radiation are recorded to produce CR during cancer therapy, opening the potential for CR to be further utilized in other high energy sources (Andreozzi, Brůža, et al., 2018; Masuda et al., 2018).

3. Cherenkov luminescence imaging (CLI)

3.1 Clinical CLI imaging utilizing Radioisotope emission

The current industry defines Cherenkov luminescence imaging (CLI) as any imaging technology that utilizes the Cherenkov radiation. The most comparable modality to CLI among widely used imaging techniques is PET. PET is able to provide images that are highly sensitive and its readings encompass the whole body. However, it is limited by poor spatial-temporal resolution, and high cost. In comparison, CLI products can achieve higher resolution at superficial depths, utilize non-radioactive dyes and are significantly cheaper and faster to produce. However, images of deeper tissues suffer with poorer resolutions. Since luminescence via CR is mostly in the ultraviolet and blue visible blue range, the light is easily absorbed and scattered by nearby tissues (Cao et al., 2015; Ciarrocchi & Belcari, 2017).

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

Therefore, although CR is thought to be useful, the current technology is limited by the type and condition of the tissue assessed.

Robertson et al. (2009), were the first to produce CR bioimages after injecting mice with 2-deoxy-2-[18F]fluoro-d-glucose (^{18}F-FDG). Highly metabolic cells such as cancer cells increase their uptake of ^{18}F-FDG as it is an analogue of glucose. ^{18}F-mediated CLI has been further applied in various studies. Notably CLI was employed to define glioblastoma tumor margins (Lewis et al., 2018). Glioblastoma is a brain tumor in which the majority of the patients require brain surgery. For the operation to be successful, the tumor border where excision occurs must include all malignant cells. Rats implanted with human glioblastoma cells were injected with either the ^{18}F-FDG probe or the control fluorescent probe. The study by Lewis et al. (2018) has found that CLI performed better than the control in determining the accurate tumor boundary.

The feasibility, safety, and performances of ^{18}F-FDG probes in determining tumor margins were also evaluated in breast-conserving surgeries (Grootendorst et al., 2017). Patients with grade 3, estrogen receptor–negative/Her-2–negative tumors all received wide excision with sentinel lymph node biopsy or axillary lymph node dissection. CLI assessed tumor margins in 10 of the 12 patients with a significant correlation found between CLI and margin histopathology. Furthermore, the procedure was performed safely through low radiation exposures to clinical staff (Grootendorst et al., 2017). ^{18}F-FDG was also used for the first clinical application of endoscopic CLI. The CCD attached to endoscopes were used to identify cancerous gastrointestinal lesions, where imaged patients received diagnostic doses of ^{18}F-FDG. CL emitted by the imaging agent showed good correlation with clinical whole-body PET imaging and allowed for the quantification and differentiation of tumors from healthy tissue (Hu et al., 2015). ^{18}F has been similarly utilized to study tumor margins of lymphoma, liver cancer, and prostate cancer (Ciarrocchi et al., 2021; Costa et al., 2022; Ritter et al., 2021).

Spinelli et al. were the first to capture CR images of a human living tissue by using ^{131}I (Spinelli et al., 2013). Thyroid specific uptake of iodine has made ^{131}I an attractive radioisotope for the image. For other tumor cells, other radioisotopes are preferred. ^{68}Ga has become especially popular due to its favorable properties, such as a short half-life of 67.7 min and 89% beta emission, and relatively low threshold compared to other radioisotopes (Naji & AL-Nahhas, 2012). A major advantage of ^{68}Ga radioisotope is the ability of the metallic ion to chelate to various proteins and antibodies. Antibodies that target specific tumor markers can be designed, allowing for greater specificity. For example, a Swedish group developed a novel PET/magnetic resonance/CR triple-modality imaging agent, ^{68}Ga-SPIONs, by labeling superparamagnetic iron oxide nanoparticles with ^{68}Ga (Madru et al., 2013). ^{68}Ga-SPIONs demonstrated accurate and sensitive Cherenkov luminescence imaging of sentinel lymph nodes (SLN) - lymph nodes near cancerous tissue. ^{68}Ga-SPION shows potential for Cherenkov luminescence to be used alongside conventional PET and MRI. In addition, the novel imaging probe ^{68}Ga-DOTAKEK-(GX1)2 was applied for PET/CR dual-modality imaging, enabling simultaneous PET and Cherenkov diagnosis for gastric cancer (Yin et al., 2021). Furthermore, a recent study reported that [^{68}Ga]Ga-PSMA-11 CR imaging could correctly identify tumor margin status in 83% of 15 prostate cancer patients, suggesting that CR imaging is a promising technique for obtaining rapid pathology results in image-guided prostate cancer surgery (J. O. Heuvel et al., 2022). Specificity and sensitivity of ^{68}Ga-chelated radioisotopes show promise and are anticipated to enter further clinical trials. In addition to ^{18}F and ^{68}Ga, other radioisotopes such as ^{47}Sc, ^{64}CU, ^{89}Zr, ^{90}Y and ^{124}I are being studied for CR mediated diagnosis and bioimaging, especially in the scope of dosimetry and monitoring radiotherapym (Bianfei et al., 2022).

In general, CRs emitted by radioisotopes are low in intensity, and most rely on charged coupled devices (CCD) or PET scanners to obtain discernable image. CCDs are popular photodetectors commonly used for digital imaging and video since the 1980s. They are designed to detect low intensity photons, through many photoactive regions made of metal-oxide-semiconductor (MOS) capacitors (Lesser, 2014). Once a capacitor interacts with photons, a surface charge is generated for that capacitor. By calculating the specific capacitors activated, and the surface charges generated, CCDs are able to translate the positional and intensity values of the photon to an image (Hui, 2020; Lesser, 2014). However, even with CCDs, the luminescence produced by the CR is dimmer than the ambient room light, and therefore requires absolute darkness to be detected. This absolute dark environmental condition is a significant disadvantage against widely utilizing CR during clinical practice.

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

3.2 Cherenkov Luminescence Tomography (CLT)

CLI is a method of two-dimensional (2D) planar imaging, which cannot provide the three-dimensional (3D) spatial distribution of the radionuclide probes (Hui, 2020; Wang et al., 2021). This problem can be solved by its 3D derivatives, such as CLT (Z. Hu et al., 2010). CLT reconstructs the spatial distribution of the internal radionuclide probes by integrating the CL images measured from the body surface with the structural information and other prior information. Li et al. first proposed the concept of CLT, reconstructing the 3D distribution of ^{18}FDG in a homogeneous mouse model (Li et al., 2010). The homogenous model is relatively simple, and is quite different from the real imaging organisms, resulting in inaccurate results. This can be solved by a more complex heterogeneous model with more defined data points as shown in Figure 4 (H. Guo et al., 2017).

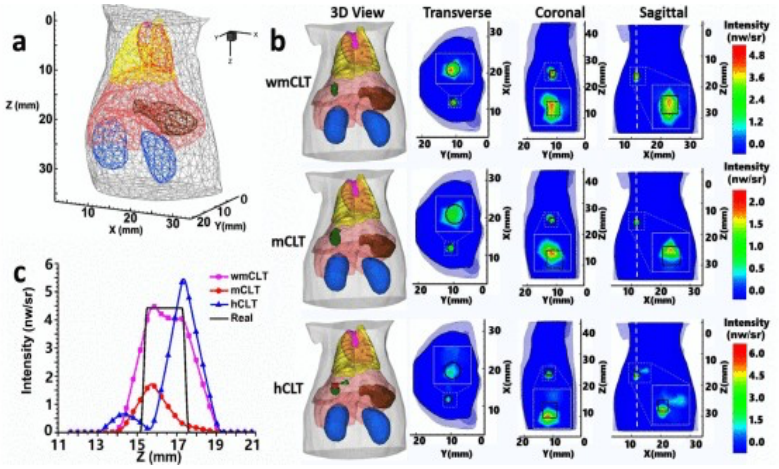

Figure 4. The multispectral representation of a xenograph tumor of various regions, a reconstruction that was possible due to weight mediated data representation. (H. Guo et al., 2017)

However, increasing the amount of measured data has the disadvantages of increasing the reconstruction time and limiting the reconstruction efficiency. Using a small amount of data to obtain accurate reconstruction results is an important problem to be addressed (Wang et al., 2021).

3.3 Cherenkov Radiation mediated Dosimetry

CR can be used for monitoring the dose and dose distribution of radiotherapy to prevent radiotherapy-related adverse events. Patients whose radiotherapies approach the eyes often experience flashes of blue and white light during the treatment (Bianfei et al., 2022). In 2008, Newman et al. concluded that the source of this light is the high-energy x-ray radiation that results in the production of CR inside the eyes (Newman et al., 2008). Since this observation, CR induced by external beam radiation therapy (EBRT) is regarded as a possible treatment and monitoring modality. EBRT delivers radiation to tumors using a linear accelerator (LINACs). The production of CR from LINACs is the same as radioisotope decay although for LINACs electrons pass through the tissue at two to three orders of magnitude higher kinetic energy. In addition, it is possible to increase photon beam energy at will, and apply beam hardening filtration for greater depth penetration than radioisotopes. These advantages strengthen LINAC's candidacy for optical molecular imaging with CR.

In 2011, Axelsson et al. captured CR images during EBRT in tissue-mimicking media and noted that the intensity of CR increased with increasing radiation energy in the same medium (Axelsson et al., 2011). Furthermore, the study has found that CR could excite the photosensitizer protoporphyrin IX, and stated the possibility of concurrent monitoring of EBRT by CR induced molecular fluorescence. Another study has utilized luminescent probe platinum oxyphor G4 (PtG4) to measure tumor oxygenation in vivo by Cherenkov-excited luminescence scanned imaging. The produced image showed submillimeter resolution and nanomolar sensitivity (Pogue et al., 2018). The use of PtG4 also allowed for the distribution values to be translated via Monte Carlo simulations to show three dimensional dose distributions. (Glaser et al., 2013). Subsequent studies have further demonstrated that dosimetry monitoring in real time for EBRT with both MV electron and x-ray beams might be possible for superficial tissues (Decker et al., 2021) Zhang et al used a time-gated intensified CCD (ICCD) that was coupled with a commercial lens to access canine oral

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

tumor (Zhang et al., 2012). The subsequent images showed that under irradiation, the intensity of Cherenkov emission is directly proportional to radiation dose (Figure 5).

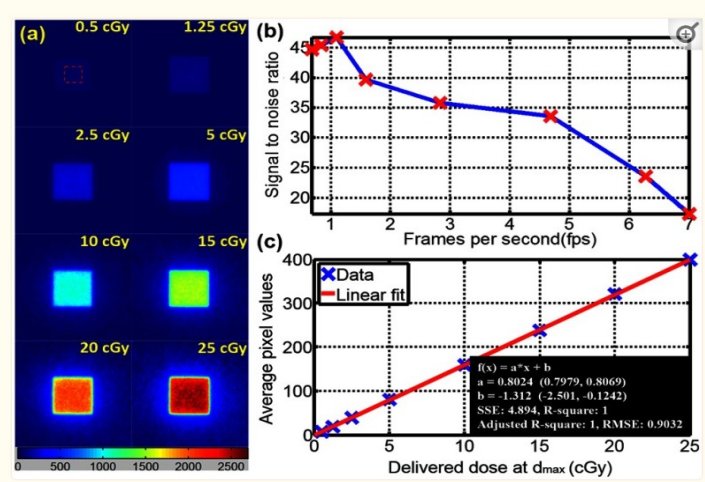

Figure 5. Images that compare the delivered dose compared with light intensity. Average pixel values and delivered dose at dmax shows direct relationship. Image obtained from (Zhang et al., 2013)

Since the use of CR produced by EBRT was established as feasible, further studies were conducted to further study the relationship between CR and radiation dose, dose depth and dose rate for accurate translation (Helo et al., 2014). Experimentally it was confirmed as the previous study that CR was linear with dose and independent of dose rate. More importantly, Cherenkov beam direction and transverse profiles showed great potential to be used to check the range and field width constancy of electron beams. This showed the potential use of CR as a monitor during radiotherapy for precise targeting of electron beams. The correlation between the diffusion of CR and its optical signal was further proven, introducing a more accurate method for verifying dose delivery in real time (Decker et al., 2021). CR imaging exhibited accurate intensity matching, suggesting that CR is suitable for quality assessment of radiation therapy that relies heavily on precise intensity (Andreozzi, Mooney, et al., 2018; Black et al., 2019; Miao et al., 2019).

The first clinical application of CR imaging in EBRT was performed on a breast cancer patient. Jarvis et al. acquired a CR video during whole-breast radiation and demonstrated the correlation between the intensity of CR and the superficial dose (Jarvis et al., 2014). Hachadorian et al. continued the whole breast imaging and improved the accuracy of CR images by reducing the noise of ambient light (Hachadorian et al., 2018). Currently CR imaging is being studied as part of the protocol to reduce variability and errors in whole-breast radiation therapy, minimizing the risk of recurrence and healthy tissue toxicity caused by inaccurate coverage (Hachadorian et al., 2021). In addition to conventional EBRT, MRI guided radiotherapy, bremsstrahlung x-rays and positron emitters were explored for CR use, with positive results (Darr et al., 2020; Jarvis et al., 2014).

Table 1. Summary of human trials involving Cherenkov Radiation

Delivery	Source	Application	Highlight	Reference
^{131}I	^{131}I	Thyroid cancer	First CR tumor diagnostic image	Spinelli et al., 2013
^{68}Ga-PSMA	^{68}Ga	Prostate cancer (after tumor cell as excised)	Tumor cells were successfully detected on the incised prostate CLI images as confirmed by histopathology.	Darr et al., 2020
^{68}Ga-PSMA	^{68}Ga	Prostate cancer, in vivo	First to demonstrate ability to distinguish between a positive and negative surgical margin, imaging within 45 min and low radiation exposure to staff	Heuvel et al., 2020
[^{68}Ga]Ga-PSMA-11	^{68}Ga	Prostate cancer	Imaging can correctly identify margin status, including close margins, in 83% of cases	Heuvel et al., 2020
LINAC	x-ray	Breast cancer	The first clinical application of CR imaging in EBRT	Zhang et al., 2013
LINAC	x-ray	Breast cancer	Whole breast imaging with more reduced visual noise.	Hachadorian et al., 2018
LINAC	x-ray	Breast cancer	Use of CR as a coupled monitoring system for accuracy of radiation beam	Hachadorian et al., 2021

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

4. Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a minimally invasive therapeutic modality that is primarily used to treat cancer (Brown et al., 2004). PDT uses two entities, a photosensitizer (PS) drug and electromagnetic radiation. PS drug's specific activation only in the presence of radiation allows for high precision (Ellis-Davies, 2007; Mayer & Heckel, 2006). Once activated PS drugs can generate cytotoxic reactive oxygen species (ROS) such as singlet oxygen (1O2) to destroy cancer cells (Clement et al., 2017). However, the majority of photoresponsive compounds react most effectively to irradiation with light showing wavelengths < 500 nm, typically showing a limiting penetration depth of only micrometers into biological tissue. Moreover, highly energetic UV light can cause harm to cells, possibly causing apoptosis or DNA damage (D'Orazio et al., 2013; Matsumura & Ananthaswamy, 2004). Cherenkov radiation (CR), which exhibits an emission spectrum in the near-UV range (250–600 nm) carries the advantage of covering the wavelength range of most photoresponsive compounds currently known (Elrick & Parker, 1968; Jelley, 1955).

Ran et al. investigated the possibility of activation based on CR generated by ^{18}F (Ran et al., 2012). Other studies have attempted to introduce novel ways to produce CR with greater penetrance and photoactivation of the PS drugs (Bulin et al., 2013; Ran et al., 2012). One study utilized ^{18}F but as a PET radiotracer, which was able to activate luciferin, a possible breast cancer treatment (Krebs et al., 2021). By demonstrating the activation and subsequent detection, the study has suggested that CR induced by therapeutic radiopharmaceuticals such as ^{90}Y could offer a possibility for a synergistic combination of radiotherapy with targeted photopharmacology in future applications. In addition, some studies employed ^{137}Cesium and ^{90}Y as a possible source for therapeutic CR (Y. Guo et al., 2020; Hartl et al., 2016). Most studies have suggested that PDT induced by Cerenkov radiation has deeper tissue penetration than traditional PDT. However, the strategy of coupling radionuclides with photosensitizers may cause severe side effects. In response, Qian et al, designed a new modality of PS drug delivery via nanovesicles, for additional protection from inaccurate activation CR due to tissue scattering (Qian et al., 2022).

5. Challenges and Future Prospects

Cherenkov Radiation is limited by half-life, faint intensity, and penetrance. As the CR process is dependent on emissions of the charged particles during decay, the speed of decay is an important factor to consider (Mc Larney et al., 2021). For example, half-life of ^{18}F (110 minutes) is not suitable for longer experimental investigations that might require days. Therefore, the choice of radioisotope to be used for clinical studies and therapy may be limited by the individual half-life. To compensate for limitation of radioisotope choice, more materials are being tested for potential use. CR is also limited by low intensity of the radiation - in the nanoWatt to picoWatt per cm2 range (Tanha et al., 2015). This characteristic is especially challenging during radioisotope-mediated CLI. The faint luminescence requires the environment to be completely dark, reducing the practicality (Bianfei et al., 2022; Tanha et al., 2015). This limitation has driven the effort to develop more sensitive CCDs that can differentiate ambient light, as well as Monte Carlo modeling to estimate minimum potential dose necessary for CLI, within the safety range (Shu et al., 2018; Tian et al., 2022). The dependence of dark has also driven exploration of CLI use in laparoscopy or endoscopy, which does not require light. Additionally, CR generated by energy modalities such as EBRT and other high energy yields does not require light control as greater kinetic energy generated results in intensity near six-fold of emitting radioisotopes (Tanha et al., 2015). Finally, the spectrum produced by CR is continuous and ranges from the UV to NIR wavelength, and its intensity is related to wavelength by $1/\lambda^2$. The most intensive CL is in the spectrum of the UV/blue band, which is easily scattered and absorbed by biological tissues (Ma et al., 2014). Therefore, only a small portion of CL emitted from the radionuclide in vivo can be detected. This resulted in most of the clinical trials currently limited to surface tumors, such as thyroid, breast, and laparoscopically, prostate and gastric cancers. However, penetrance is shown to be greater for EBRT, and further research will aim towards evaluating new probes that produce more penetrating light.

6. Conclusion

Since its first use in biomedical sciences, Cherenkov radiation has emerged as an attractive new modality for safe

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

and cost efficient bioimaging compared to conventional imaging technologies. While the first decade was limited mostly to animal models, an increasing number of studies have conducted human clinical trials to better marginalize the tumors for surgical excisions. There is a growing trend of evolving radioisotopes that can simultaneously be detected by PET, MRI and CR related CCD. Further, three-dimensional imagery of CR is being refined through a new modality known as Cherenkov luminescence tomography (CLT). In addition to vast research dedicated to diagnostics, photodynamic therapy utilizing CR is also receiving more attention, due to their higher penetrance compared to conventional therapies. Currently, all the advanced CR related applications in oncology are in the clinical trial stages, and more time is needed to see full clinical potential. Developing tracers or probes that can produce longer lasting CR with greater intensities, and developing scanners that can detect faint signatures will further cement the place of CR in the growing field of cancer molecular imaging.

References

Andreozzi, J. M., et al. (2018). Improving treatment geometries in total skin electron therapy: Experimental investigation of linac angles and floor scatter dose contributions using Cherenkov imaging. *Medical Physics*, *45*(6), 2639–2646. https://doi.org/10.1002/mp.12917

Andreozzi, J. M., et al. (2018). Remote Cherenkov imaging-based quality assurance of a magnetic resonance image-guided radiotherapy system. *Medical Physics*, *45*(6), 2647–2659. https://doi.org/10.1002/mp.12919

Axelsson, J., et al. (2011). Cerenkov emission induced by external beam radiation stimulates molecular fluorescence. *Medical Physics*, *38*(7), 4127–4132. https://doi.org/10.1118/1.3592646

Bianfei, S., et al. (2022). Application of Cherenkov radiation in tumor imaging and treatment. *Future Oncology*, *18*(27), 3101–3118. https://doi.org/10.2217/fon-2022-0022

Black, P. J., et al. (2019). An investigation of clinical treatment field delivery verification using cherenkov imaging: IMRT positioning shifts and field matching. *Medical Physics*, *46*(1), 302–317. https://doi.org/10.1002/mp.13250

Brown, S. B., Brown, E. A., & Walker, I. (2004). The present and future role of photodynamic therapy in cancer treatment. *The Lancet. Oncology*, *5*(8), 497–508. https://doi.org/10.1016/S1470-2045(04)01529-3

Bulin, A.-L., et al. (2013). X-ray-Induced Singlet Oxygen Activation with Nanoscintillator-Coupled Porphyrins. *The Journal of Physical Chemistry C*, *117*(41), 21583–21589. https://doi.org/10.1021/jp4077189

Cao, X., et al. (2015). Intensity Enhanced Cerenkov Luminescence Imaging Using Terbium-Doped Gd2O2S Microparticles. *ACS Applied Materials & Interfaces*, *7*(22), 11775–11782. https://doi.org/10.1021/acsami.5b00432

Chen, Z., Lu, W., Garcia-Prieto, C., & Huang, P. (2007). The Warburg effect and its cancer therapeutic implications. *Journal of Bioenergetics and Biomembranes*, *39*(3), 267–274. https://doi.org/10.1007/s10863-007-9086-x

Ciarrocchi, E., & Belcari, N. (2017). Cerenkov luminescence imaging: Physics principles and potential applications in biomedical sciences. *EJNMMI Physics*, *4*(1), 14. https://doi.org/10.1186/s40658-017-0181-8

Ciarrocchi, E., et al. (2021). In-vitro Study for Cerenkov Luminescence Imaging Application in Hepatic Metastasectomy. *Frontiers in Physics*, *9*. https://www.frontiersin.org/articles/10.3389/fphy.2021.635540

Clement, S., et al. (2017). Nanoparticle-mediated singlet oxygen generation from photosensitizers. *Journal of Photochemistry and Photobiology A: Chemistry*, *332*, 66–71. https://doi.org/10.1016/j.jphotochem.2016.08.009

Costa, P. F., et al. (2022). F18-PSMA Cerenkov luminescence and flexible autoradiography Imaging in a prostate cancer mouse model and first results of a radical prostatectomy feasibility study in men. *Journal of Nuclear Medicine*. https://doi.org/10.2967/jnumed.122.264670

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

Darr, C., et al. (2020). Intraoperative 68Ga-PSMA Cerenkov Luminescence Imaging for Surgical Margins in Radical Prostatectomy: A Feasibility Study. *Journal of Nuclear Medicine*, *61*(10), 1500–1506. https://doi.org/10.2967/jnumed.119.240424

Das, P. R., & Boruah, K. (2022). Gamma hadron separation method in ground-based gamma ray astronomy using simulated data. *Indian Journal of Physics*. https://doi.org/10.1007/s12648-022-02423-y

Decker, S. M., et al. (2021). Estimation of diffuse Cherenkov optical emission from external beam radiation build-up in tissue. *Journal of Biomedical Optics*, *26*(9), 098003. https://doi.org/10.1117/1.JBO.26.9.098003

D'Orazio, J., et al. (2013). UV Radiation and the Skin. *International Journal of Molecular Sciences*, *14*(6), Article https://doi.org/10.3390/ijms140612222

Ellis-Davies, G. C. R. (2007). Caged compounds: Photorelease technology for control of cellular chemistry and physiology. *Nature Methods*, *4*(8), Article 8. https://doi.org/10.1038/nmeth1072

Elrick, R. H., & Parker, R. P. (1968). The use of Cerenkov radiation in the measurement of β-emitting radionuclides. *The International Journal of Applied Radiation and Isotopes*, *19*(3), 263–271. https://doi.org/10.1016/0020-708X(68)90023-9

Glaser, A. K., et al. (2013). Projection imaging of photon beams by the Čerenkov effect. *Medical Physics*, *40*(1), 012101. https://doi.org/10.1118/1.4770286

Grootendorst, M. R., et al. (2017). Intraoperative Assessment of Tumor Resection Margins in Breast-Conserving Surgery Using 18F-FDG Cerenkov Luminescence Imaging: A First-in-Human Feasibility Study. *Journal of Nuclear Medicine*, *58*(6), 891–898. https://doi.org/10.2967/jnumed.116.181032

Guo, H., et al. (2017). Weight Multispectral Reconstruction Strategy for Enhanced Reconstruction Accuracy and Stability With Cerenkov Luminescence Tomography. *IEEE Transactions on Medical Imaging*, *36*(6), 1337–1346. https://doi.org/10.1109/TMI.2017.2658661

Guo, Y., et al. (2020). Photodynamic Therapy Excited by Cerenkov Radiation from Cesium-137 Irradiator: In Vitro Studies. *Clinical Oncology and Research*, *2020*(6), 1–5. https://doi.org/10.31487/j.COR.2020.06.07

Hachadorian, R., et al. (2018). Correcting Cherenkov light attenuation in tissue using spatial frequency domain imaging for quantitative surface dosimetry during whole breast radiation therapy. *Journal of Biomedical Optics*, *24*(7), 071609. https://doi.org/10.1117/1.JBO.24.7.071609

Hachadorian, R., et al. (2021). Verification of field match lines in whole breast radiation therapy using Cherenkov imaging. *Radiotherapy and Oncology*, *160*, 90–96. https://doi.org/10.1016/j.radonc.2021.04.013

Hartl, B. A., et al. (2016). Activating Photodynamic Therapy in vitro with Cerenkov Radiation Generated from Yttrium-90. *Journal of Environmental Pathology, Toxicology and Oncology : Official Organ of the International Society for Environmental Toxicology and Cancer*, *35*(2), 185–192. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2016016903

Helo, Y., et al. (2014). Imaging Cerenkov emission as a quality assurance tool in electron radiotherapy. *Physics in Medicine & Biology*, *59*(8), 1963. https://doi.org/10.1088/0031-9155/59/8/1963

Hernot, S., et al. (2019). Latest developments in molecular tracers for fluorescence image-guided cancer surgery. *The Lancet Oncology*, *20*(7), e354–e367. https://doi.org/10.1016/S1470-2045(19)30317-1

Heuvel, J. O., et al. (2022). Cerenkov Luminescence Imaging in Prostate Cancer: Not the Only Light That Shines. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *63*(1), 29–35. https://doi.org/10.2967/jnumed.120.260034

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

Hu, H., et al. (2015). Feasibility study of novel endoscopic Cerenkov luminescence imaging system in detecting and quantifying gastrointestinal disease: First human results. *European Radiology*, *25*(6), 1814–1822. https://doi.org/10.1007/s00330-014-3574-2

Hu, Z., et al. (2010). Experimental Cerenkov luminescence tomography of the mouse model with SPECT imaging validation. *Optics Express*, *18*(24), 24441–24450. https://doi.org/10.1364/OE.18.024441

Hui, R. (2020). Chapter 4—Photodetectors. In R. Hui (Ed.), *Introduction to Fiber-Optic Communications* (pp. 125–154). Academic Press. https://doi.org/10.1016/B978-0-12-805345-4.00004-4

Jadvar, H. (2016). Is There Use for FDG-PET in Prostate Cancer? *Seminars in Nuclear Medicine*, *46*(6), 502–506. https://doi.org/10.1053/j.semnuclmed.2016.07.004

Jarvis, L. A., et al. (2014). Cherenkov Video Imaging Allows for the First Visualization of Radiation Therapy in Real Time. *International Journal of Radiation Oncology*Biology*Physics*, *89*(3), 615–622. https://doi.org/10.1016/j.ijrobp.2014.01.046

Jelley, J. V. (1955). Cerenkov radiation and its applications. *British Journal of Applied Physics*, *6*(7), 227. https://doi.org/10.1088/0508-3443/6/7/301

Khan, R., et al. (2021). Refractive index of biological tissues: Review, measurement techniques, and applications. *Photodiagnosis and Photodynamic Therapy*, *33*, 102192. https://doi.org/10.1016/j.pdpdt.2021.102192

Krebs, M., et al. (2021). Photopharmacological Applications for Cherenkov Radiation Generated by Clinically Used Radionuclides. *International Journal of Molecular Sciences*, *22*(16), Article 16. https://doi.org/10.3390/ijms22169010

Lesser, M. (2014). 3—Charge coupled device (CCD) image sensors. In D. Durini (Ed.), *High Performance Silicon Imaging* (pp. 78–97). Woodhead Publishing. https://doi.org/10.1533/9780857097521.1.78

Lewis, D. Y., et al. (2018). [18F]fluoroethyltyrosine-induced Cerenkov Luminescence Improves Image-Guided Surgical Resection of Glioma. *Theranostics*, *8*(14), 3991–4002. https://doi.org/10.7150/thno.23709

Li, C., Mitchell, G. S., & Cherry, S. R. (2010). Cerenkov Luminescence Tomography for Small Animal Imaging. *Optics Letters*, *35*(7), 1109–1111.

Ma, X., Wang, J., & Cheng, Z. (2014). Cerenkov radiation: A multi-functional approach for biological sciences. *Frontiers in Physics*, *2*. https://www.frontiersin.org/articles/10.3389/fphy.2014.00004

Madru, R., et al.. (2013). 68Ga-labeled superparamagnetic iron oxide nanoparticles (SPIONs) for multi-modality PET/MR/Cherenkov luminescence imaging of sentinel lymph nodes. *American Journal of Nuclear Medicine and Molecular Imaging*, *4*(1), 60–69.

Masuda, T., et al. (2018). Measurement of nuclear reaction cross sections by using Cherenkov radiation toward high-precision proton therapy. *Scientific Reports*, *8*(1), Article 1. https://doi.org/10.1038/s41598-018- 20906-z

Matsumura, Y., & Ananthaswamy, H. N. (2004). Toxic effects of ultraviolet radiation on the skin. *Toxicology and Applied Pharmacology*, *195*(3), 298–308. https://doi.org/10.1016/j.taap.2003.08.019

Mayer, G., & Heckel, A. (2006). Biologically Active Molecules with a "Light Switch." *Angewandte Chemie International Edition*, *45*(30), 4900–4921. https://doi.org/10.1002/anie.200600387

Mc Larney, B., Skubal, M., & Grimm, J. (2021). A Review of Recent and Emerging Approaches for the Clinical Application of Cerenkov Luminescence Imaging. *Frontiers in Physics*, *9*. https://www.frontiersin.org/articles/10.3389/fphy.2021.684196

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

Miao, T., et al. (2019). Cherenkov imaging for linac beam shape analysis as a remote electronic quality assessment verification tool. *Medical Physics*, *46*(2), 811–821. https://doi.org/10.1002/mp.13303

Naji, M., & AL-Nahhas, A. (2012). ^{68}Ga-labelled peptides in the management of neuroectodermal tumours. *European Journal of Nuclear Medicine and Molecular Imaging*, *39 Suppl 1*, S61-67. https://doi.org/10.1007/s00259-011-1990-y

Newman, F., et al. (2008). Visual sensations during megavoltage radiotherapy to the orbit attributable to Cherenkov radiation. *Medical Physics*, *35*(1), 77–80. https://doi.org/10.1118/1.2815358

Heuvel, J., et al. (2020). 68Ga-PSMA Cerenkov luminescence imaging in primary prostate cancer: First-in-man series. *European Journal of Nuclear Medicine and Molecular Imaging*, *47*(11), 2624–2632. https://doi.org/10.1007/s00259-020-04783-1

Pogue, B. W., et al. (2018). Maps of in vivo oxygen pressure with submillimetre resolution and nanomolar sensitivity enabled by Cherenkov-excited luminescence scanned imaging. *Nature Biomedical Engineering*, *2*(4), Article 4. https://doi.org/10.1038/s41551-018-0220-3

Qian, R., et al. (2022). Minimizing adverse effects of Cerenkov radiation induced photodynamic therapy with transformable photosensitizer-loaded nanovesicles. *Journal of Nanobiotechnology*, *20*(1), 203. https://doi.org/10.1186/s12951-022-01401-0

Ran, C., et al. (2012). In Vivo Photoactivation Without "Light": Use of Cherenkov Radiation to Overcome the Penetration Limit of Light. *Molecular Imaging and Biology*, *14*(2), 156–162. https://doi.org/10.1007/s11307-011-0489-z

Ritter, Z., et al. (2021). In situ lymphoma imaging in a spontaneous mouse model using the Cerenkov Luminescence of F-18 and Ga-67 isotopes. *Scientific Reports*, *11*(1), Article 1. https://doi.org/10.1038/s41598-021-03505- 3

Robertson, R., et al. (2009). Optical imaging of Cerenkov light generation from positron-emitting radiotracers. *Physics in Medicine and Biology*, *54*(16), N355-365. https://doi.org/10.1088/0031-9155/54/16/N01

Rowe, S. P., & Pomper, M. G. (2022). Molecular imaging in oncology: Current impact and future directions. *CA: A Cancer Journal for Clinicians*, *72*(4), 333–352. https://doi.org/10.3322/caac.21713

Shu, D.-Y., et al. (2018). Analysis on the emission and potential application of Cherenkov radiation in boron neutron capture therapy: A Monte Carlo simulation study. *Applied Radiation and Isotopes*, *137*, 219–224. https://doi.org/10.1016/j.apradiso.2018.04.012

Spinelli, A. E., et al. (2013). First human Cerenkography. *Journal of Biomedical Optics*, *18*(2), 020502. https://doi.org/10.1117/1.JBO.18.2.020502

Tanha, K., Pashazadeh, A. M., & Pogue, B. W. (2015). Review of biomedical Čerenkov luminescence imaging applications. *Biomedical Optics Express*, *6*(8), 3053–3065. https://doi.org/10.1364/BOE.6.003053

Tian, F., et al. (2022). Proton range monitoring based on picosecond detection using a Cherenkov radiation detector: A Monte Carlo study. *Applied Radiation and Isotopes*, *180*, 110055. https://doi.org/10.1016/j.apradiso.2021.110055

Wang, L., He, X., & Yu, J. (2021). Prior Compensation Algorithm for Cerenkov Luminescence Tomography From Single-View Measurements. *Frontiers in Oncology*, *11*. https://www.frontiersin.org/articles/10.3389/fonc.2021.749889

Wilson, M. P., et al. (2020). Diagnostic accuracy of 99mTc-sestamibi SPECT/CT for detecting renal oncocytomas and other benign renal lesions: A systematic review and meta-analysis. *Abdominal Radiology*, *45*(8), 2532–2541. https://doi.org/10.1007/s00261-020-02469-8

Vol. 2023 (2) 214 – 225
ISSN 2688-3651 [online]

Yin, J., et al. (2021). 68Ga-Labeled GX1 Dimer: A Novel Probe for PET/Cerenkov Imaging Targeting Gastric Cancer. *Frontiers in Oncology*, *11*. https://www.frontiersin.org/articles/10.3389/fonc.2021.750376

Zhang, R., et al. (2013). Real-time in vivo Cherenkoscopy imaging during external beam radiation therapy. *Journal of Biomedical Optics*, *18*(11), 110504. https://doi.org/10.1117/1.JBO.18.11.110504

Zhang, R., et al. (2012). Čerenkov radiation emission and excited luminescence (CREL) sensitivity during external beam radiation therapy: Monte Carlo and tissue oxygenation phantom studies. *Biomedical Optics Express*, *3*(10), 2381–2394. https://doi.org/10.1364/BOE.3.002381