Eur Radiol
DOI 10.1007/s00330-014-3574-2

MOLECULAR IMAGING

Feasibility study of novel endoscopic Cerenkov luminescence imaging system in detecting and quantifying gastrointestinal disease: first human results

Hao Hu · Xin Cao · Fei Kang · Min Wang · Yenan Lin · Muhan Liu · Shujun Li · Liping Yao · Jie Liang · Jimin Liang · Yongzhan Nie · Xueli Chen · Jing Wang · Kaichun Wu

Received: 9 April 2014 / Revised: 8 December 2014 / Accepted: 17 December 2014

Abstract

Objectives Cerenkov luminescence imaging (CLI) provides potential to use clinical radiotracers for optical imaging. The goal of this study was to present a newly developed endoscopic CLI (ECLI) system and illustrate its feasibility and potential in distinguishing and quantifying cancerous lesions of the GI tract.

Methods The ECLI system was established by integrating an electron-multiplying charge-coupled device camera with a flexible fibre endoscope. Phantom experiments and animal studies were conducted to test and illustrate the system in detecting and quantifying the presence of radionuclide in vitro and in vivo. A pilot clinical study was performed to evaluate our system in clinical settings.

Results Phantom and mice experiments demonstrated its ability to acquire both the luminescent and photographic images with high accuracy. Linear quantitative relationships were also obtained when comparing the ECLI radiance with the radiotracer activity (r^2=0.9779) and traditional CLI values (r^2= 0.9025). Imaging of patients revealed the potential of ECLI in the identification and quantification of cancerous tissue from normal, which showed good consistence with the clinical PET examination.

Conclusions The new ECLI system shows good consistence with the clinical PET examination and has great potential for clinical translation and in aiding detection of the GI tract disease.

Key Points

- *CLI preserves the characteristics of both optical and radionuclide imaging.*
- *CLI provides great potential for clinical translation of optical imaging.*
- *The newly developed endoscopic CLI (ECLI) has quantification and imaging capacities.*
- *GI tract has accessible open surfaces, making ECLI a potentially suitable technique.*
- *Cerenkov endoscopy has great clinical potential in detecting GI disease.*

Hao Hu, Xin Cao and Fei Kang contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00330-014-3574-2) contains supplementary material, which is available to authorized users.

H. Hu · S. Li · L. Yao · J. Liang · Y. Nie · K. Wu (✉)
State Key Laboratory of Cancer Biology, Department of Digestive Diseases, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China
e-mail: kaicwu228@gmail.com

X. Cao · Y. Lin · M. Liu · J. Liang · X. Chen (✉)
School of Life Science and Technology, Xidian University, Xi'an 710071, China
e-mail: xlchen@xidian.edu.cn

F. Kang · J. Wang (✉)
Department of Nuclear Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China
e-mail: wangjing@fmmu.edu.cn

M. Wang
Department of Gastroenterology, Xi'an Children's Hospital, Xi'an, China

Keywords Molecular imaging · Radionuclide imaging · Optical imaging · Endoscopy · Gastrointestinal disease

Abbreviations

CLI	Cerenkov luminescence imaging
CLT	Cerenkov luminescence tomography
ECLI	Endoscopic Cerenkov luminescence imaging
EMCCD	Electron-multiplying charge-coupled device
GI	Gastrointestinal

Published online: 11 January 2015

Introduction

Because of the excellent advantages of cost-effectiveness, high sensitivity and relatively high throughput compared with the traditional nuclear imaging technology, Cerenkov luminescence imaging (CLI) has become a promising and powerful preclinical imaging technique [1–3]. The CLI technology detects a radionuclide with the optical imaging techniques based on Cerenkov radiation; that is, when charged particles travel in a dielectric medium with a speed exceeding the phase velocity of light, visible and near-infrared light is emitted [4]. CLI was first introduced for in vivo imaging in 2009 [5]. Since then CLI has shown its inherent potential as a novel imaging tool. In 2012, the first human CLI study was reported by Spinelli et al., which further paved the way for the development of CLI [6]. Currently, CLI has proved useful in a wide range of applications from preclinical studies to clinical applications such as monitoring the uptake of ^{18}F-FDG and ^{131}I, detecting thyroid cancer and evaluating the treatment of lymphoma [7–14].

However, because Cerenkov light can only penetrate 1–2 cm owing to its heavy attenuation in tissues [15], conventional CLI devices can hardly be used in imaging the deeper and internal lesions. To overcome this limitation, an interesting approach combining CLI devices with a flexible optical fibre was reported by Cheng et al. [13]. Through combination with a flexible optical fibre (Schott-75), the Cerenkov signal can be transferred from a remote or deep location and then detected by the CCD camera. Their work was the first to demonstrate the experimental feasibility of using CLI for intraoperative imaging, and suggested a possibility of using the CLI for deeper and internal imaging.

In this study, we developed a novel endoscopic system for CLI (the ECLI system) and demonstrated its clinical potential in deeper gastrointestinal disease. This ECLI system was established by integrating an electron-multiplying charge-coupled device (EMCCD) camera with a flexible fibre endoscope. This system can simultaneously provide both the luminescent and photographic images and has seamless integration. These features facilitate endoscopy manipulation, lesion identification as well as quantification regardless of ambient light interference. To illustrate the feasibility of the ECLI system, phantom experiments, animal studies and a pilot human trial were conducted. In addition, quantitative relationships between the ECLI signals and activity of radionuclides were investigated. Our results suggested that the ECLI system combined with diagnostic doses of ^{18}F-FDG are feasible and have a good consistence with disease assessment by traditional clinical PET examination. To the best of our knowledge, this study is the first in vivo application of the ECLI system in gastrointestinal (GI) disease.

Materials and methods

Endoscopic Cerenkov luminescence imaging system (ECLI)

All the system elements were assembled and established in our laboratory. Our system consists of three parts, an EMCCD camera (iXon 3-888, Andor), a clinical flexible fibre endoscope (LF-TP, Olympus) and an optical adaptor. The EMCCD can be controlled by an external computer. The fibre endoscope field of view is 90°, and the direction of view is 0° (forward). The spatial resolution is 0.35 lp/mm [16]. The optical adaptor, developed in our lab, was used to seamlessly connect the EMCCD and endoscope. All the images acquired by ECLI and traditional CLI systems were presented on the scale of radiance, which is converted by the grey value in a greyscale image [12, 17].

Quantitative formula

In order to achieve comparable and accurate quantitative analysis of the images acquired by our ECLI system, a preliminary quantitative formula was established according to the performance parameters of the ECLI system and the Lambertian source theory [18]. Using the quantitative formula, one can convert the intensity on the EMCCD camera (dimensionless quantities) into the number of photons incident on the detector surface (in units of photons per second per square-centimetre per solid angle):

$$R=\frac{(I+B)A_m}{G_{EM}Q}\frac{1}{s_p t}\frac{\pi\left(d^2+r^2\right)}{s_e}$$

where R is the number of emitted photons incident on the detector surface, which is in units of ph s^{-1} cm^{-2} sr^{-1}; I is the dimensionless intensity imaged on the EMCCD camera; B denotes the minus bias offset which is the electronic bias offset of the CCD camera and the value was fixed at 100 for the adopted EMCCD; A_m is preamplifier of the EMCCD camera with the value of 5.1; G_{EM} is electron-multiplying gain and was set to be 1,000 in the following luminescence imaging experiments; Q is the quantum efficiency (QE) of transforming photons into electrons, which depends on the wavelength of light, and the value reached up to 96 % for the wavelengths used in our experiments; s_p is the area of the cell in the EMCCD camera, which is a product of the CCD's pixel area and binning value (set to be 4 in our experiments), with a unit of cm^2; t is the exposure time in the luminescence imaging experiments and in units of second; d is distance between the front probe of the fibre endoscope and the detected surface; r and s_e are radius and areas of the front probe of the fibre endoscope, respectively.

Phantom experiments

As a proof of concept, a phantom experiment was conducted to validate the ability of the ECLI system to acquire both the luminescent and photographic images. In the experiment, a piece of paper with a Chinese character (4×4 mm) printed on it was fixed on the surface of a holder. A droplet of ^{18}F-FDG liquid (0.185 MBq, 5 μCi) was dropped on the left corner of the character. The white light and Cerenkov luminescent images were taken by our ECLI system separately (distance 5 mm). For the linearity and quantification study, eight different radioactivities of ^{18}F-FDG solutions (12.5, 24.3, 35.4, 45.9, 55.9, 65.2, 74.1 and 82.4 μCi) were imaged by ECLI.

Pseudotumour model

^{18}F-FDG was produced by cyclotron (GE Industries Inc.) and an FDG reagent kit (ABX). Animal care and protocols were approved by the Fourth Military Medical University Animal Studies Committee. Eight-week-old female nude mice were anaesthetized by intraperitoneal (ip) injection of 0.2 ml of ketamine/xylazine (30 mg ketamine combined with 2 mg of xylazine in a 4-ml volume). The pseudotumour model was conducted on living animals as described in previous studies [19–21]. Briefly, a 70-μL mixture of 3.7 MBq (100 μCi) of ^{18}F-FDG and 30 μL Matrigel (BD Biosciences) was injected subcutaneously. Mice were kept on a warm bed during the ECLI examination.

Patients

As rectal cancer is easier to probe with our endoscopic system, four patients were chosen between June and October 2013. Patients aged 40–60 years and prescribed an ^{18}F-FDG examination for diagnosis and metastasis detection were considered eligible for inclusion in the study. Patients with a history of surgical resection of the proximal colon (caecum, ascending colon and transverse colon) were excluded from this study. Patients with inflammatory bowel disease (IBD), familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) were also considered as ineligible for the study.

Examination procedure

Colonoscopy preparation was performed as described previously [22]. Briefly, patients consumed a regular meal for lunch and clear liquids for dinner the day before colonoscopy. They drank two sachets of polyethylene glycol 4000 electrolytes powder (WanHe Pharmaceutical Co, Shenzhen, China) dissolved in 2 L of water between 4.00 am and 5.00 am within 2 h of the colonoscopy on the same day of the colonoscopy. Before the ECLI examination, patients were given ^{18}F-FDG intravenously (9.25 MBq/kg, 0.25 mCi/kg). Patients first underwent whole-body PET, and then transferred to a dark room for ECLI examination. Scopolamine butylbromide (10 mg) was administered intravenously to avoid bowel movements prior to examination for the patients with no contraindication to the use of this agent. To avoid unnecessary harm and reduce examination time, a clinical colonoscope was first inserted to locate the tumour, and then the endoscopic end of the ECLI was inserted parallel to the colonoscope. The whole insertion process was guided by both colonoscope monitor and ECLI monitor. The ECLI images were acquired for 5 min with a binning value of 4, and biopsy samples were taken at the end. The endoscopic examination procedure was performed by an experienced doctor, Kaichun Wu.

Ethical considerations

The study was approved by the institutional review board of Xijing Hospital, Fourth Military Medical University (FMMU). Written informed consent for examination and treatment were obtained from all of the studied patients prior to the procedures.

Results

ECLI system

A schematic of the developed ECLI system is illustrated in Fig. 1. The system consists of three parts, a flexible fibre endoscope, an optical adaptor and an EMCCD. A micro-sized objective lens fitted at the distal end of the fibre endoscope was used to acquire the Cerenkov luminescent signal as well as the white-light signal. An LED lamp provided white-light illumination. A light-tight optical adaptor was adopted to seamlessly integrate the fibre endoscope and the EMCCD, and protected the whole system from the ambient light. The EMCCD, with a peak quantum efficiency of 90 % working in a low temperature mode (−80 °C) to reduce the electronic noise, was employed to collect the weak Cerenkov luminescent and photographic signals. In addition, the EMCCD has a dynamic video imaging function. The image in the field of view (FOV) of the fibre endoscope can be directly screened on an external controlled computer, which could assist endoscopists in locating normal and cancerous tissues. The prototype of the ECLI system is shown in Supplementary Fig. S1.

Phantom experiments

In order to investigate the feasibility of the ECLI system in acquiring both Cerenkov luminescent and white-light

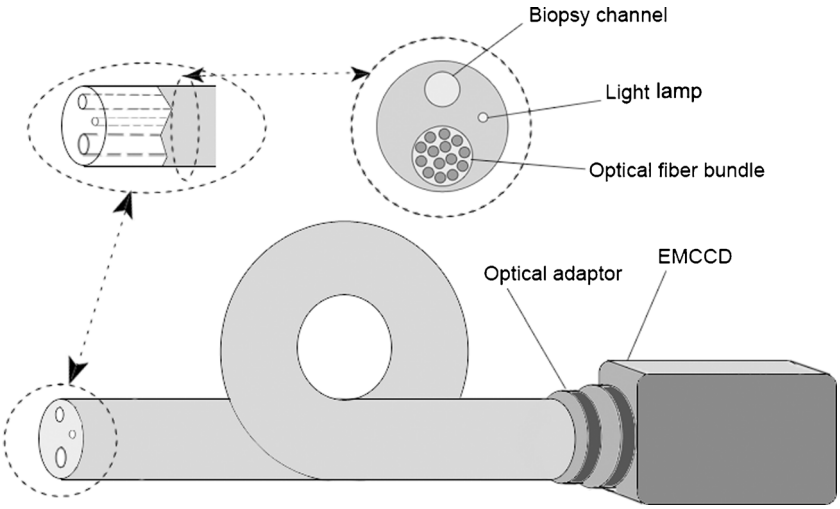

Fig. 1 Schematic diagram of the developed ECLI system

images, a phantom experiment was conducted. About 0.185 MBq (5 μCi) of ^{18}F-FDG was dropped onto a piece of paper on which a Chinese character was printed (Fig. 2a). After placing the endoscopy unit in front of the object (5 mm), a white-light photographic image which was first acquired with an exposure time of 0.01 s (Fig. 2b, c). Then, we turned off the LED lamp, and the Cerenkov luminescent image was obtained with 5 min exposure (Fig. 2d). Since the relative position of the phantom and the ECLI system remained unchanged during the acquisition, we directly overlapped the luminescent and photographic images (Fig. 2e). To further identify the ECLI radiance as an indicator of the sample's radioactivity, a linear quantitative study was carried out. The ECLI system collected the light emitted from eight different concentrations of ^{18}F-FDG (Fig. 3a), and a linear quantitative relation between the ECLI radiance and the radiotracer radioactivity (r^2=0.9779, Fig. 3b) was successively established. To exclude the influence of radiation scintillation, a shielding experiment was performed. Thus 70 μCi of ^{18}F-FDG solution was imaged by ECLI with and without a piece of black paper, respectively. Our data showed that the black paper covering can significantly block the Cerenkov signals (Supplementary Fig. S2).

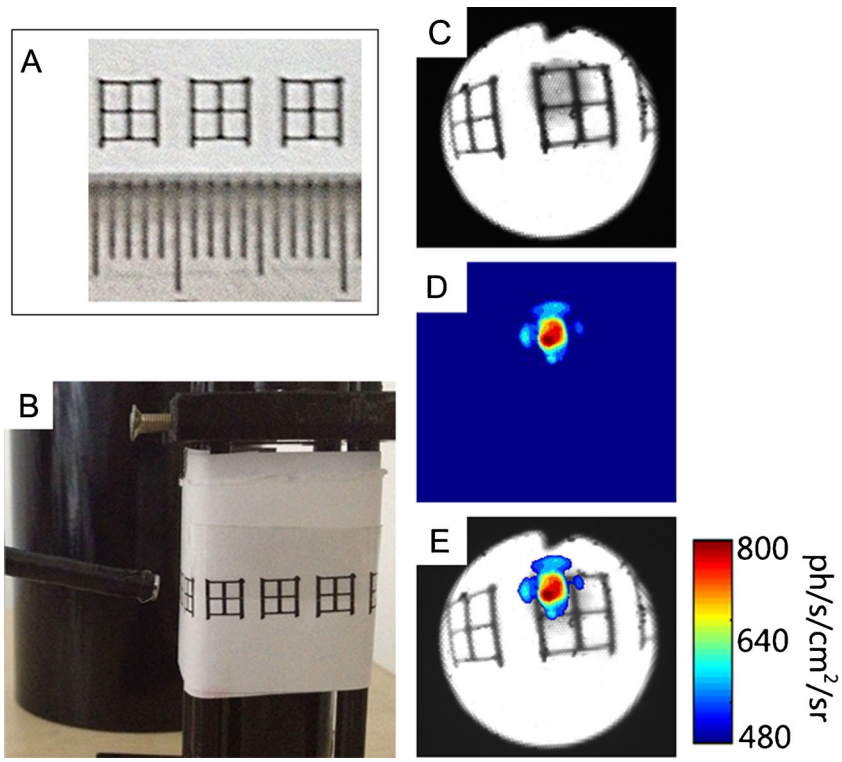

Fig. 2 Phantom experiment. **a** Chinese character measuring 4× 4 mm^2 printed on paper. **b** A distance of about 5 mm between the distal end and the paper. **c** White-light image acquired by the ECLI system, the *shadow* on the image is ^{18}F-FDG. **d** Cerenkov luminescent image acquired by the ECLI system, where the image was coloured coded in Matlab 2012R2 (MathWorks Corp). **e** Overlay image of the white-light and Cerenkov luminescent images

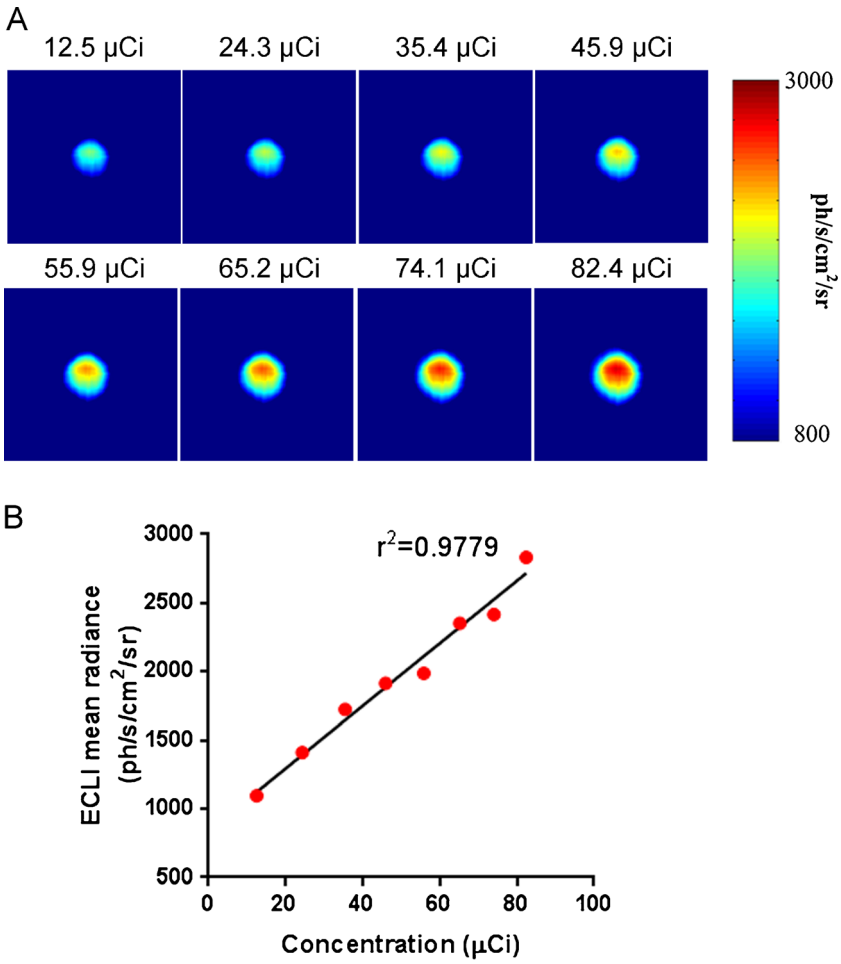

Fig. 3 Linear quantitative relationship study. **a** Representative ECLI images of different concentration of ^{18}F-FDG. **b** Linear quantitative relationship between the ECLI radiance and the ^{18}F-FDG concentration

Pseudotumour study

During the pseudotumour experiment, mice were anaesthetized and fixed on a warm platform made of black organic glass. Firstly, a traditional whole-body CLI system was used to acquire images (Fig. 4a, n=4). After that, the same mouse was immediately examined by the ECLI system (Fig. 4b, n=4). As shown in Fig. 4, both the traditional CLI and our developed ECLI system could detect the Cerenkov luminescent signals emitted from the pseudotumour. Importantly, our ECLI system showed a good consistence with the traditional CLI system, which can be observed from the linear quantitative relation with a robust correlation index of r^2=0.9025 (Fig. 4c).

Pilot human trial

To demonstrate the feasibility and potential of the ECLI system in the clinical setting, a human pilot trial was conducted. Informed consent was gained from each patient. Patients' information is listed in Supplementary Table S1. For each patient, whole-body PET imaging was first carried out, and then patients were transferred to a dark room for ECLI examination. In four patients, three had PET positive responses, and one was negative. During ECLI imaging, the cold light source of the ECLI endoscope was shut off to produce a dark environment. In order to verify the ability of quantification between normal and cancerous tissues, Cerenkov luminescent images at both cancerous and normal tissues were collected (Fig. 5a). Figure 5b shows white-light images taken by clinical colonoscopy, in which Cerenkov luminescent signals in Fig. 5a were incorporated and our ECLI fibre endoscopy can be seen. The corresponding PET/CT images of the same patient are shown Fig. 5c.

In all three PET-positive patients, radiance of the malicious region was higher than that of normal surroundings. The cancerous tissue showed a mean radiance value of 791±77.02, compared with the normal tissue of 585.3±38.89 (P=0.0144, Fig. 6). In the PET-negative patient, whose tissue biopsy later indicated moderate mucosa inflammation, no difference in radiance was observed between "cancerous" and normal tissues. A distinct difference between the cancerous and normal tissues observed in Cerenkov luminescent images indicated a

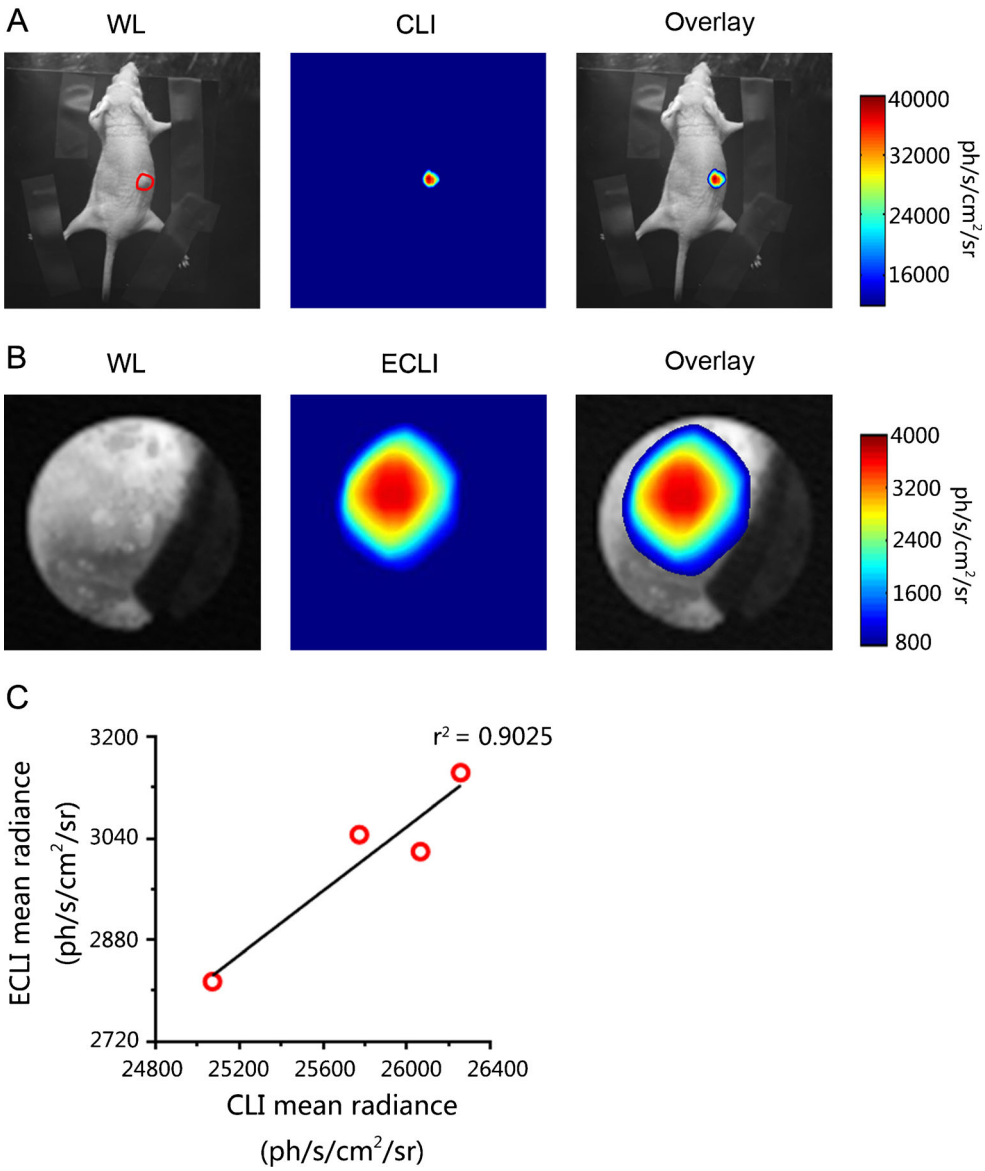

Fig. 4 Results of the in vivo pseudotumor study. **a** Representative images taken by the traditional CLI system, where the *red circle* indicates the region of the pseudotumor. **b** Representative images acquired by the ECLI system. **c** Correlation analysis between the traditional CLI and ECLI system, $n=4$

good consistence with the PET results and suggested the great potential of our developed ECLI system in clinical applications.

Discussion

In this study, a novel endoscopic system for Cerenkov luminescence imaging (ECLI system) was developed and a series of in vitro and in vivo experiments were conducted to validate its feasibility. Results from the in vitro phantom experiments demonstrated the ability of the system to simultaneously provide both luminescent and photographic images, and showed a good linear quantitative relation between the Cerenkov luminescent signals and the radiotracer activity (r^2=0.9779, Fig. 3b). Results from the pseudotumour experiment suggested a good performance of our ECLI system in the applications of in vivo studies. Patients' results revealed the ability of the ECLI system to distinguish cancerous tissue from normal tissue.

CLI is an emerging and noninvasive optical imaging technology which uses PET tracers as its probes. This imaging technique has spurred considerable interests in the use of a radioactive source for optical imaging [23], since it was quickly demonstrated in living mice [12]. CLI has been validated with many advantages, such as high sensitivity, low cost, wide availability, relatively high throughput and commercially available radionuclide probes already approved for human use [3]. However, regarding the clinical translation from preclinical studies to human use, legitimate concerns about the clinical usage of CLI may be raised. More specifically, its penetration is the most challenging part of CLI imaging.

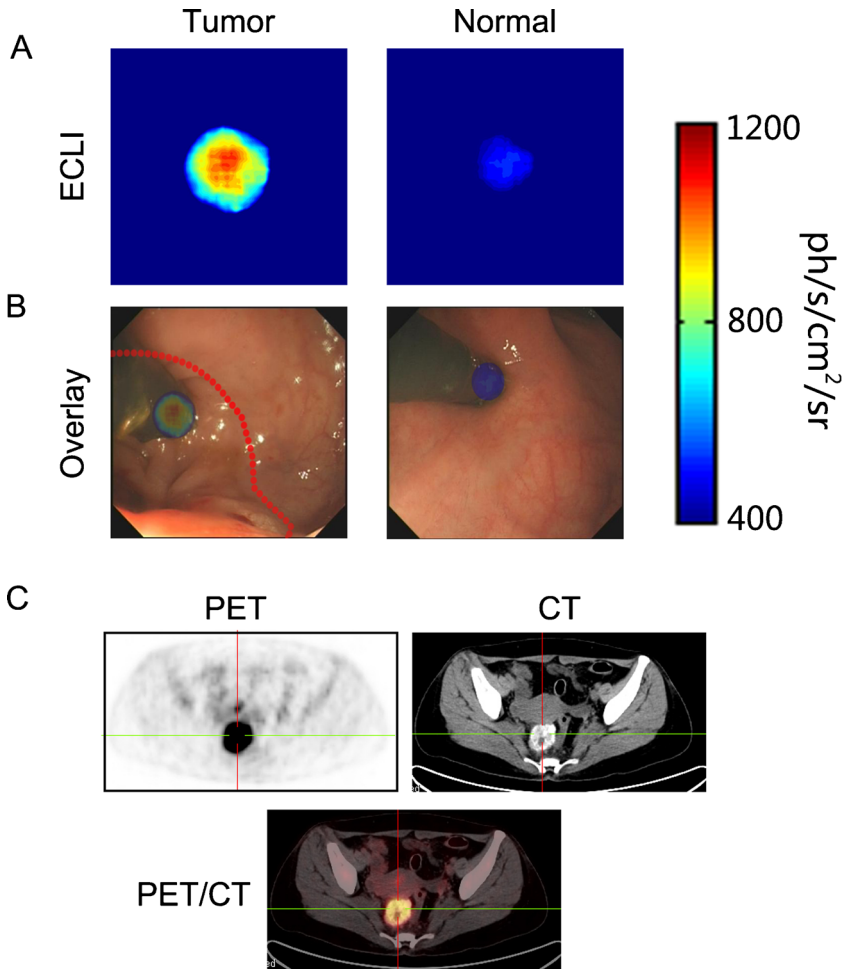

Fig. 5 Representative results for the human pilot trial in which PET/CT images indicated an ^{18}F-FDG-positive tumor. **a** Cerenkov luminescent image of the cancerous and normal tissues. **b** ECLI images overlaid with white-light photographs. **c** PET/CT results from the same patient. *Red dashed line* tumorous region

Indeed, the Cerenkov luminescent light is very weak. The Cerenkov luminescent light produced by positron emitters is several orders of magnitude weaker than fluorescent imaging, which is again several orders lower than the ambient light [24]. Currently, CLI clinical usage has mainly been confined to superficial imaging and requires a relatively rigorous dark environment; for instance, using diagnostic ^{131}I for imaging disease in the thyroid gland [6] and ^{18}F-FDG scans to detect nodal disease [24].

What about using CLI in detecting disease of the gastrointestinal (GI) tract? Actually, the environment of the gastrointestinal tract is very suitable for CLI. Firstly, the surface of the GI tract is open and accessible. Endoscopy can easily reach the locus of the lesion. In addition, most of the GI lesions, such

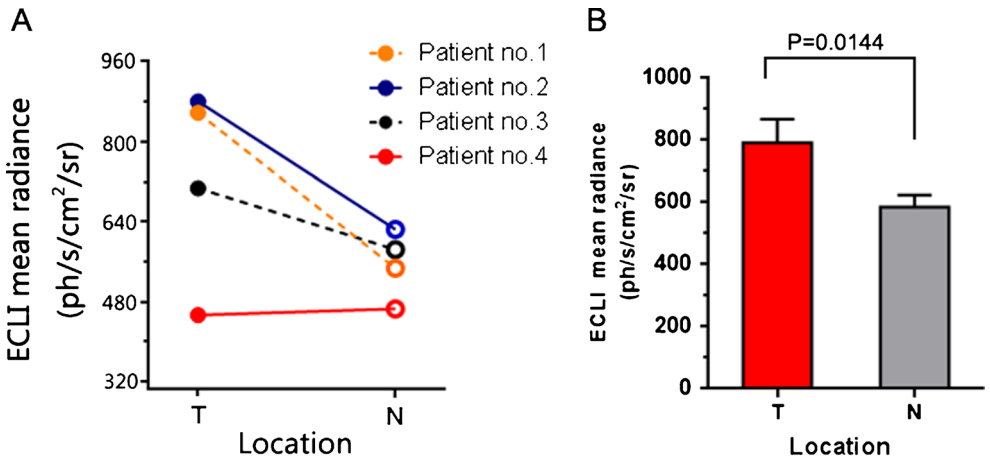

Fig. 6 **a** ECLI mean radiance of 4 patients. *T* tumorous region, *N* normal surroundings. **b** Statistical analysis of radiance from tumorous and nomal tissue (*t* test)

as polyps and GI tumours, are often integrated with the lumen. In other words, the GI lesion in the GI tract is "superficial" and "reachable". Thus, these unique traits actually bypass the crucial disadvantage of CLI i.e. "limited penetration". Secondly, the surrounding environment of the GI lumen is totally dark, which can avoid the interference of the Cerenkov luminescent signals. Compared with other diseases, such as thyroid and axillary node disease, there is no need to take ambient light into consideration, which is always a big issue with applications of CLI. On the basis of the above description, we developed an endoscopy method based on CLI, called the ECLI system, for GI disease detection. In fact, not confined to the diseases of the GI tract, the ECLI system can also be applied to other system diseases when equipped with different kinds of endoscopes, such as bronchial disease with a bronchoscope, uterine disease with a hysteroscope, and identifying abdominal metastatic lymph nodes with a laparoscope. Combined with new developed probes and radiotracers, ECLI can allow both morphological and functional examinations (Cerenkov imaging) in the same endoscopic examination. Therefore, the ECLI system has great potential in terms of translation to clinical applications.

In our experiment, even though a good and quantitative linear correlation was obtained by using the ECLI system, we noticed that there was significant signal attenuation compared with CLI. For example, in our pseudotumour experiment, the mean radiance of the ROI in the traditional CLI image was about 25,071.44, which is about nine times larger than the ECLI value of around 2,814.88. This might be caused by the following two reasons. Firstly, incoming light is reduced because of the small diameter of our endoscope. The incoming signal that could reach the EMCCD was greatly reduced. While the traditional direct CLI system used a normal optical lens, which had a relatively larger aperture, it allowed the collection of more optical signals. Secondly, the system suffers from inherent attenuation of light transmission in the optical fibre. Therefore, the use of an increased acquisition time or different endoscope with a larger diameter may improve the signal attenuation.

In addition, during the acquisition of the Cerenkov luminescent signal, the EMCCD camera was set to be in electron-multiplying mode with a value of 1,000, which led to the EMCCD camera being more sensitive than the traditional CCD camera. However, there were also γ-photons emitted from the radiotracer. Once these high-energy photons hit the EMCCD camera, an undesired noise would appear in the luminescent images. In order to remove these noise points, a median filter template of 10×10 was used to preprocess the luminescent images (Supplementary Fig. S3).

The cost of ECLI should be taken into account during system development; further work concentrated on the improvement of imaging sensitivity and resolution could help to reduce the amount of radiotracer, and thus the patients' radiation exposure and cost. With the development of molecular imaging technology, we believe that the ECLI system can be translated into clinical applications, especially for gastrointestinal examination, as a useful tool for disease detection and resection monitoring.

Conclusion

In this study, we successfully established an ECLI system, and demonstrated its feasibility and potential for clinical translation. In the phantom experiments, our ECLI system showed a good linear quantitative relationship with the ^{18}F-FDG concentration. In addition, the ability to acquire both the Cerenkov luminescent and white-light images was demonstrated. In the animal studies, consistent results were obtained using our ECLI system compared with the transitional CLI. The human pilot trial, in addition, further validated the great potential of ECLI in future clinical applications.

Acknowledgments The scientific guarantor of this publication is Xueli Chen at Xidian University. The authors would like to thank Dr. Xiaowei Ma from Department of Nuclear Medicine, Xijing Hospital, Fourth Military Medical University for the technical assistance. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. This work was supported in part by the National Natural Science Foundation of China under Grant Nos. 81090270, 81090272, 81090273, 81101083, 81230033, 81371615 and 81370585; Program of the National Basic Research and Development Program of China (973) under Grant Nos. 2011CB707702, 2010CB529302, the National Municipal Science and Technology Project under Grant Nos. 2009ZX09103-667, 2009ZX09301-009-RC06, and the Open Research Project under Grant 20120101 from SKLMCCS. No complex statistical methods were necessary for this paper. Institutional review board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Approval from the institutional animal care committee was obtained. Methodology: experimental, performed at one institution.

References

1. Ruggiero A, Holland JP, Lewis JS, Grimm J (2010) Cerenkov luminescence imaging of medical isotopes. J Nucl Med 51:1123–1130
2. Spinelli AE, D'Ambrosio D, Calderan L, Marengo M, Sbarbati A, Boschi F (2010) Cerenkov radiation allows in vivo optical imaging of positron emitting radiotracers. Phys Med Biol 55:483
3. Xu Y, Liu H, Cheng Z (2011) Harnessing the power of radionuclides for optical imaging: Cerenkov luminescence imaging. J Nucl Med 52:2009–2018
4. Jelley J (1955) Cerenkov radiation and its applications. Br J Appl Phys 6:227
5. Robertson R, Germanos MS, Li C, Mitchell GS, Cherry SR, Silva MD (2009) Optical imaging of Cerenkov light generation from positron-emitting radiotracers. Phys Med Biol 54:N355–N365
6. Spinelli AE, Ferdeghini M, Cavedon C et al (2013) First human Cerenkography. J Biomed Opt 18:020502

7. Boschi F, Calderan L, D'Ambrosio D et al (2011) In vivo 18F-FDG tumour uptake measurements in small animals using Cerenkov radiation. Eur J Nucl Med Mol Imaging 38:120–127
8. Hu Z, Ma X, Qu X et al (2012) Three-dimensional noninvasive monitoring iodine-131 uptake in the thyroid using a modified Cerenkov luminescence tomography approach. PLoS ONE 7:e37623
9. Jeong SY, Hwang M-H, Kim JE et al (2011) Combined Cerenkov luminescence and nuclear imaging of radioiodine in the thyroid gland and thyroid cancer cells expressing sodium iodide symporter: initial feasibility study. Endocr J 58:575
10. Robertson R, Germanos MS, Manfredi MG, Smith PG, Silva MD (2011) Multimodal imaging with 18F-FDG PET and Cerenkov luminescence imaging after MLN4924 treatment in a human lymphoma xenograft model. J Nucl Med 52:1764–1769
11. Li C, Mitchell GS, Cherry SR (2010) Cerenkov luminescence tomography for small animal imaging. Opt Lett 35:1109–1111
12. Hu Z, Liang J, Yang W et al (2010) Experimental Cerenkov luminescence tomography of the mouse model with SPECT imaging validation. Opt Express 18:24441–24450
13. Liu H, Carpenter CM, Jiang H et al (2012) Intraoperative imaging of tumors using Cerenkov luminescence endoscopy: a feasibility experimental study. J Nucl Med 53:1579–1584
14. Kothapalli S-R, Liu H, Liao JC, Cheng Z, Gambhir SS (2012) Endoscopic imaging of Cerenkov luminescence. Biomed Opt Express 3:1215
15. Ma X, Yang W, Zhou S et al (2012) Study of penetration depth and resolution of Cerenkov luminescence emitted from (18)F-FDG and (131)I. J Nucl Med 53:55
16. China Food and Drug Administration, imported instrument database history (2006) http://app1.sfda.gov.cn/datasearch/face3/dir.html. Accessed 5 Apr 2014
17. Thorek DL, Ogirala A, Beattie BJ, Grimm J (2013) Quantitative imaging of disease signatures through radioactive decay signal conversion. Nat Med 19:1345–1350
18. Chen X, Gao X, Chen D et al (2010) 3D reconstruction of light flux distribution on arbitrary surfaces from 2D multi-photographic images. Opt Express 18:19876–19893
19. Dothager RS, Goiffon RJ, Jackson E, Harpstrite S, Piwnica-Worms D (2010) Cerenkov radiation energy transfer (CRET) imaging: a novel method for optical imaging of PET isotopes in biological systems. PLoS ONE 5:e13300
20. Liu H, Zhang X, Xing B, Han P, Gambhir SS, Cheng Z (2010) Radiation-luminescence-excited quantum dots for in vivo multiplexed optical imaging. Small 6:1087–1091
21. Carpenter CM, Sun C, Pratx G, Liu H, Cheng Z, Xing L (2012) Radioluminescent nanophosphors enable multiplexed small-animal imaging. Opt Express 20:11598
22. Luo H, Zhang L, Liu X et al (2013) Water exchange enhanced cecal intubation in potentially difficult colonoscopy. Unsedated patients with prior abdominal or pelvic surgery: a prospective, randomized, controlled trial. Gastrointest Endosc 77:767–773
23. Xu Y, Chang E, Liu H, Jiang H, Gambhir SS, Cheng Z (2012) Proof-of-concept study of monitoring cancer drug therapy with cerenkov luminescence imaging. J Nucl Med 53:312–317
24. Thorek DL, Riedl C, Grimm J (2014) Clinical Cerenkov luminescence imaging of 18F-FDG. J Nucl Med 55:95–98