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A novel Foley catheter made of high-intensity near-infrared fluorescent silicone rubber for image-guided surgery of lower rectal cancer

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ABSTRACT

Background: Urethral injury occurs in 1–6 % of male cases during minimally invasive surgery of lower rectal cancer. A Foley catheter emitting near-infrared (NIR) fluorescence of sufficient intensity has been expected to locate the urethra during image-guided surgery. Although it has been difficult to impart NIR fluorescent properties to biocompatible thermosetting polymers, we have recently succeeded in developing a NIR fluorescent compound for silicone rubber and a NIR fluorescent Foley catheter (HICARL). Here, we evaluated its NIR fluorescence properties and visibility performance using porcine anorectal isolation specimens.

Methods: The HICARL catheter was made of a mixture of solid silicone rubber and a NIR fluorescent compound that emits fluorescence with a wavelength of 820–880 nm, while a conventional transparent Foley catheter was made of solid silicone rubber only. As a standard for comparison of the intensity of NIR fluorescence, a transparent Foley catheter the lumen of which was filled with a mixture of indocyanine green (ICG) and human plasma was used. As a comparison to assess the visibility performance of the HICARL catheter, a transparent Foley catheter into which a commercially available NIR fluorescent polyurethane ureteral catheter (NIRC) was placed was used.

Results: A NIR fluorescence quantitative imaging analysis revealed that the Foley-NIRC catheter and the HICARL catheter emitted 3.42 ± 0.42 and 6.43 ± 0.07 times more fluorescence than the Foley-ICG catheter, respectively. The location of the HICARL catheter placed in the anorectum with a wall thickness of 3.8 ± 0.1 mm was clearly delineated in its entirety by NIR fluorescence, while that of the Foley-NIRC catheter was faintly or only partially visible.

Conclusions: The HICARL catheter emitting NIR fluorescence of sufficient intensity is a promising and easy-to-use tool for urethral visualization during image-guided surgery of lower rectal cancer.

1. Introduction

Transanal total mesorectal excision (TaTME) is a minimally invasive approach for the radical treatment of lower rectal cancer [1], but TaTME is a complex procedure in male patients. Urethral injury has been reported to occur in 1 % to 6 % of cases when incising the rectus-urethralis muscle close to the urethra [2–5]. Therefore, intraoperative urethral visualization methods utilizing the high tissue permeability of near-infrared (NIR) light and fluorescence have been proposed. In the NIR light method using an illuminated ureteral stent (IRIS U-Kits, Stryker, Kalamazoo, MI, USA), a set of optical fiber and a transparent catheter for guiding the fiber were passed through a transparent silicone Foley catheter placed in the urethra, and the optical fiber was connected to an external laser light source with a wavelength of 830 nm. Atallah et al. demonstrated that the urethra was transilluminated by the illuminated ureteral stent in a cadaveric model [6]. However, the illuminated ureteral stent in the urethra was visible only in a dark field and not under normal white light. Surgical procedures in a dark field are often dangerous, and the use of illuminated ureteral stents for trans-illumination of the urethra has not been approved by the FDA.

Barnes et al. used NIR fluorescence imaging to successfully identify the urethra in cadavers during TaTME procedures by injecting a mixture of indocyanine green (ICG) and lubricant gel directly into the urethra [7] or by filling the lumen of a transparent silicone Foley catheter with a coagulating mixture of ICG and ethanol [8]. However, intraurethral injection of ICG has not been approved by the FDA, and filling Foley

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catheters interferes with urine volume monitoring. Therefore, these methods do not appear to be clinically practical.

Our method of incorporating NIR fluorescent dyes with thermoplastic resins [9] has led to the development of indwelling devices, such as clips [10] and catheters [11], for NIR fluorescence-guided surgery. Kisu et al. demonstrated a clinical usefulness of NIR fluorescent polyurethane ureteral catheters (NIRC, Cardinal Health Japan, Tokyo, Japan) for the real-time intraoperative visualization of the ureters during gynecological laparoscopic surgery [12]. A case report by Onishi et al. showed that a 6-Fr NIRC ureteral catheter placed in the urethra was useful for detection of the urethra in a 3-kg male neonate with anorectal malformation during laparoscopy-assisted anorectoplasty [13]. When this method is applied to adult males, who have thicker urethras than neonates, a transparent silicone Foley catheter with a pre-inserted NIRC ureteral catheter can offer an intraoperative tool to visualize the urethra without the need for connection to an external light source. More promising, however, is a Foley catheter made of NIR fluorescent silicone rubber and having the same structure and implantation method as a conventional Foley catheter.

Although it has been difficult to impart NIR fluorescent properties to biocompatible thermosetting polymers [14], we have succeeded in developing a NIR fluorescent compound for silicone rubber and a NIR fluorescent Foley catheter. Here, we evaluated its fluorescent properties by bench performance tests and assessed its visualization performance using porcine anorectal isolation specimens.

2. Materials and methods

This study was performed under the approval of the Animal Research Committee of the Kobe Medical Device Development Center (permit No. IVT22–113). Written consent was not needed, as this study did not include human subjects.

2.1. Conventional transparent Foley catheters and HICARL catheters

A newly developed NIR fluorescent Foley catheter (HICARL, Mizuho, Tokyo, Japan) was made of a mixture of solid silicone rubber and a proprietary NIR fluorescent compound that emits fluorescence at a wavelength of 820–880 nm in response to excitation light at a wavelength of 740–800 nm, while a conventional transparent Foley catheter was made of solid silicone rubber only. The 14-Fr size tubes were manufactured using an extrusion and thermosetting system. All materials used passed physical property and biocompatibility testing in accordance with medical regulatory standards.

2.2. Foley-NIRC catheters

A conventional 14-Fr transparent Foley silicone catheter into which a NIRC ureteral polyurethane catheter was placed was used as a comparison to evaluate the visibility performance of the HICARL catheter. Since NIRC ureteral catheters are only commercially available in the 6-Fr size [11,12], a 14-Fr Foley catheter with an inner diameter of 2.4–2.6 mm was selected to fit a NIRC ureteral catheter. The transparent Foley catheter with a pre-inserted NIRC ureteral catheter is hereafter referred to as the “Foley-NIRC catheter”.

2.3. Foley-ICG catheters

A mixture of ICG (Diagnogreen, Daiichi Sankyo, Tokyo, Japan) and human plasma (Cosmo Bio USA, Carlsbad, CA, USA) at a final concentration of 10 μg/mL, which emits its brightest fluorescence [15], was prepared as a standard for comparing the intensity of NIR fluorescence. The transparent Foley catheter with ICG plasma solution sealed in the lumen is hereafter referred to as the “Foley-ICG catheter”.

2.4. Bench performance tests

The NIR fluorescence brightness of the conventional transparent Foley catheter, the Foley-ICG catheter, the Foley-NIRC catheter, and the HICARL catheter was measured with a NIR fluorescence quantitative imaging system (FL View, Nirec, Kochi, Japan). Each sample was placed on an optical absorption sheet (Super Black IR, Shibuya Optical, Wako, Japan) so that background noise caused by the reflection of the excitation light that transmitted through the catheters was reduced to less than 1.6 %. The wavelength of the excitation light was set to 780 nm. The irradiance at the sample surface was adjusted to 30 mW/cm^2. NIR fluorescence at a wavelength of 820–880 nm was measured and analyzed.

2.5. Visibility performance assessment with anorectal isolation specimens

Porcine anorectal isolation specimens were purchased from the Kobe Medical Device Development Center. The visibility performance of NIR fluorescence emitted by the Foley-NIRC catheter and the HICARL catheter implanted in the anorectum was evaluated with a custom-made laparoscopic system that simultaneously images visible light and NIR fluorescence [9]. In the overlay image of visible light and NIR fluorescence, the NIR fluorescence was shown in green. The irradiance of the excitation laser light at a wavelength of 780 nm was adjusted to 15 or 30 mW/cm^2 at the center of the tissue surface while the irradiance was measured with an optical power meter system (model 8230 and 82311B, ADC, Saitama, Japan). The laparoscopic working distance was set to 50 mm. NIR fluorescence at a wavelength of 820–880 nm was detected with a fixed exposure time of 1/30 second, and the brightness of NIR fluorescence was analyzed using ImageJ Version 1.54d. On an 8-bit grayscale NIR fluorescence image with a resolution of 1280 horizontal pixels by 1020 vertical pixels, a circular region with a diameter of 40 pixels centered on the highest point of brightness was set as the region of interest. For each NIR fluorescence image, the average value of the brightness within the region of interest was calculated as the visibility performance score. After laparoscopic observation of each catheter, the thickness of the anorectal wall on the catheter was measured with an ultrasound system (Vscan, GE Healthcare, Chicago, IL, USA).

2.6. Statistical analysis

Statistical analysis between independent groups was performed by Mann-Whitney U test or Steel-Dwass multiple comparison test using Kyplot Version 4.0.1 (KyensLab, Tokyo, Japan). Paired difference tests for repeated measures in a single sample were performed by the Wilcoxon signed-rank test. Differences were considered significant at $p < 0.05$. Values are expressed as mean ± SD.

3. Results

An overall view of the NIRC ureteral catheter, Foley-NIRC catheter, and HICARL catheter is shown in Fig. 1; for the Foley-NIRC catheter, the NIRC ureteral catheter is visible through the transparent Foley catheter. Fig. 2 shows representative examples of 8-bit grayscale images of the transparent Foley catheter, Foley-ICG catheter, Foley-NIRC catheter, and HICARL catheter during excitation light exposure. No fluorescence was observed from the transparent Foley catheter. Scaling the mean NIR fluorescence brightness of the Foley-ICG catheter to 1, the NIR fluorescence brightness of the Foley-NIRC catheter was 3.42 ± 0.42 and that of the HICARL catheter was 6.43 ± 0.42. (Fig. 3). Of these three types of NIR fluorescent catheters, the HICARL catheter was the most significantly brighter ($p < 0.05$, $n = 5$ for each group).

The visibility performance of the Foley-NIRC catheter and HICARL catheter implanted in the porcine anorectum with a wall thickness of 3.8 ± 0.1 mm was evaluated with a custom-made laparoscopic imaging system. Fig. 4 shows representative examples of visible light (RGB),

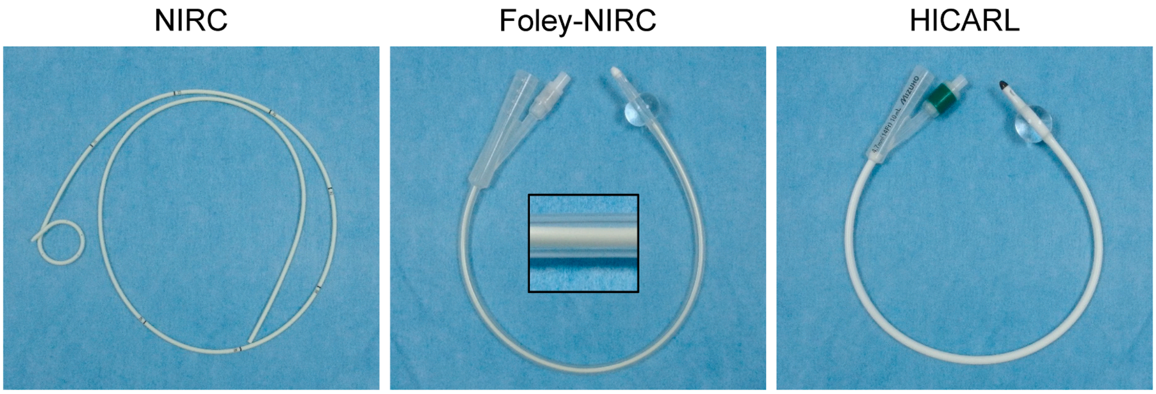

Fig. 1. Photographs showing an overall view of the NIRC ureteral catheter, Foley-NIRC catheter, and HICARL catheter. In an inset showing a magnified image of the Foley-NIRC catheter, the NIRC ureteral catheter is visible through the transparent Foley catheter.

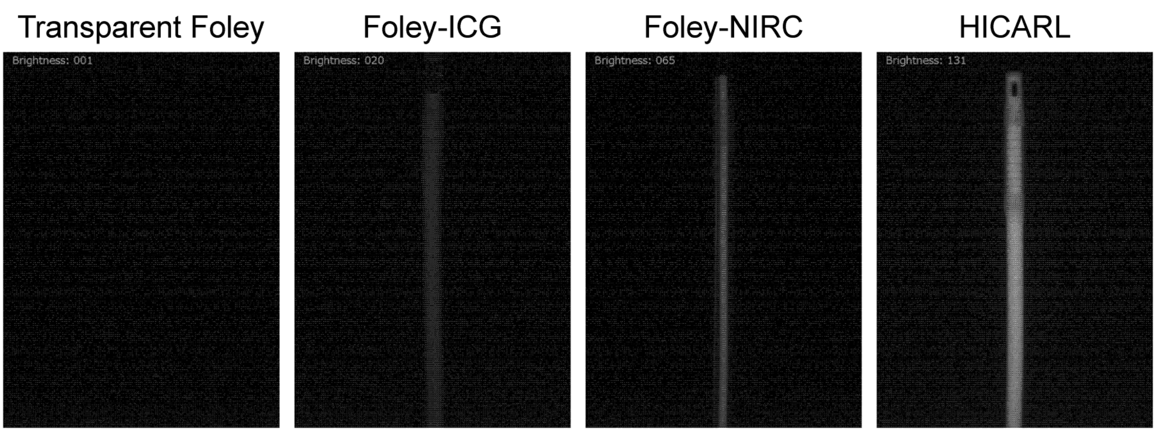

Fig. 2. Representative examples of 8-bit grayscale images of the transparent Foley catheter, Foley-ICG catheter, Foley-NIRC catheter, and HICARL catheter during irradiation of excitation light. Each sample was placed on a light absorption sheet, so that background noise due to unwanted diffuse reflection of excitation light and repetitive emission of NIR fluorescence was less than 1.6 % in the wavelength range of 250 nm to 2500 nm. No fluorescence was observed from the transparent Foley catheter.

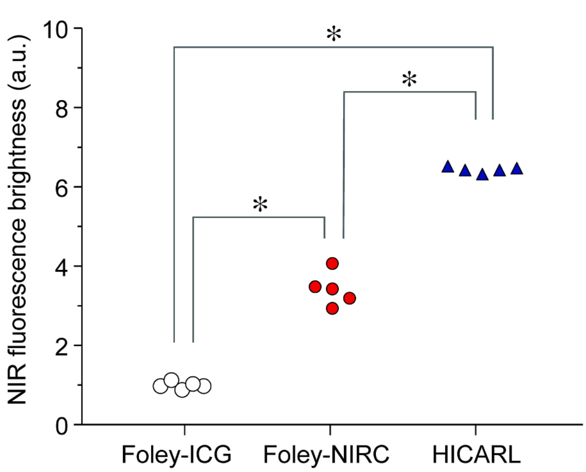

Fig. 3. Graph showing NIR fluorescence brightness of the Foley-ICG catheter (white filled circles), Foley-NIRC catheter (red filled circles), and HICARL catheter (blue filled triangles) during irradiation of excitation light. The average value of NIR fluorescence brightness of the Foley-ICG catheter was scaled to 1. *$p < 0.05$, $n = 5$ for each group. a.u., arbitrary units.

overlay (RGB-NIR), and 8-bit grayscale fluorescence (NIR) images under weak (15 mW/cm^2) and strong (30 mW/cm^2) excitation light. Both catheters could be located on NIR fluorescence images, but the Foley-NIRC catheter required more intense excitation light exposure. The results of the evaluation of the two types of catheters are summarized in Fig. 5. For both types of catheters, the level of excitation light exposure significantly affected the intensity of NIR fluorescence ($p < 0.05$, $n = 5$ for paired samples). At all irradiation levels, the HICARL catheter had significantly higher visibility performance scores than the Foley-NIRC catheter ($p < 0.05$, $n = 5$ for each group).

4. Discussion

In the present study, we evaluated NIR fluorescence properties of a newly developed HICARL catheter by bench performance tests and assessed its visibility performance with isolated preparations of the porcine anorectum. The results suggest that the HICARL catheter is a promising tool for intraoperative urethral visualization by NIR fluorescence imaging.

Recently, two approaches to visualize the urethra by NIR fluorescence imaging have been reported; i.e., an intraurethral ICG injection method [7] and a method using a transparent silicone Foley catheter in which NIR fluorescent materials are sealed or packed [8]. However, both approaches have several drawbacks. First, a direct injection of ICG into the urethra has not been approved. Second, repeated injections of ICG into the urethra during several hours of anorectal surgery are not practical clinically. Third, narrowing and occluding the lumen of Foley catheters by sealing or packing with NIR fluorescent materials would impede urine flow. Taken together with these points, Foley catheters that emit NIR fluorescence without compromising an original function

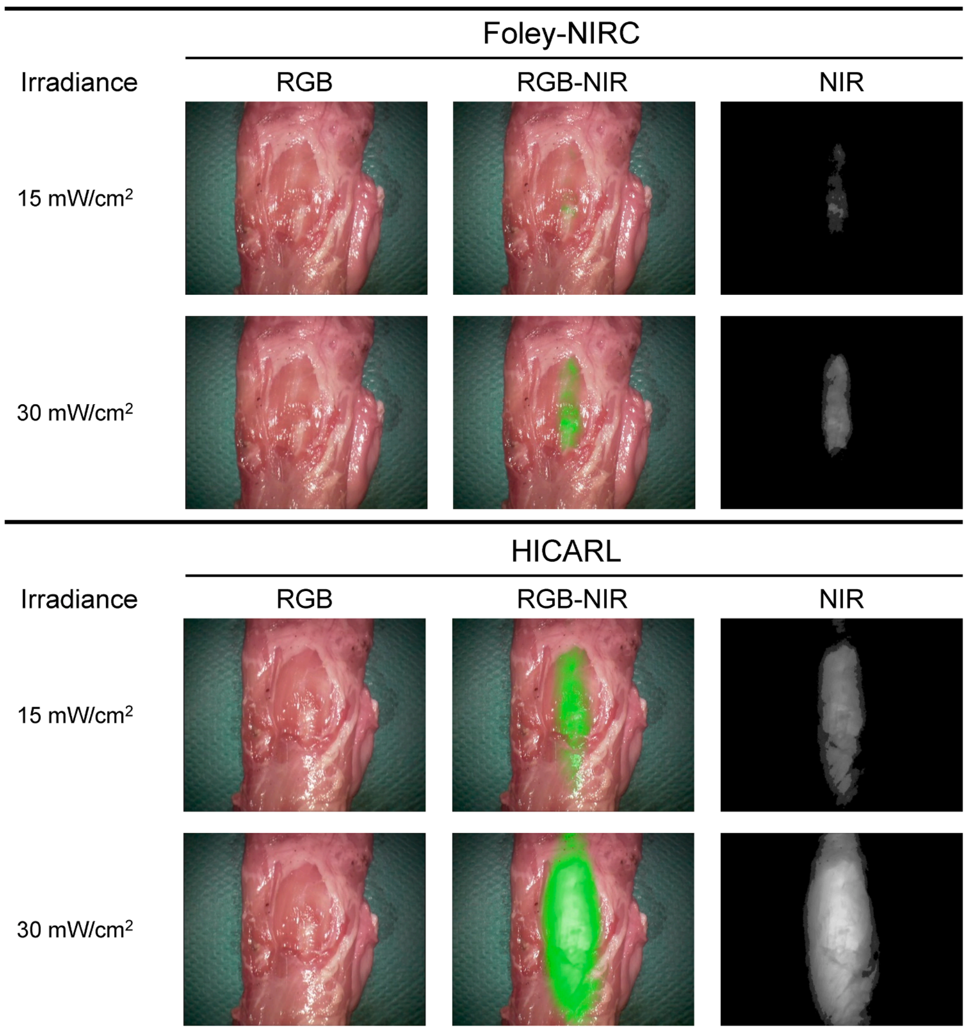

Fig. 4. Representative examples of visible light (RGB), overlay (RGB-NIR), and 8-bit grayscale fluorescence (NIR) images of the Foley-NIRC catheter and HICARL catheter during weak (15 mW/cm^2) and strong (30 mW/cm^2) irradiation of excitation light. In the overlay image, the NIR fluorescence is shown in green.

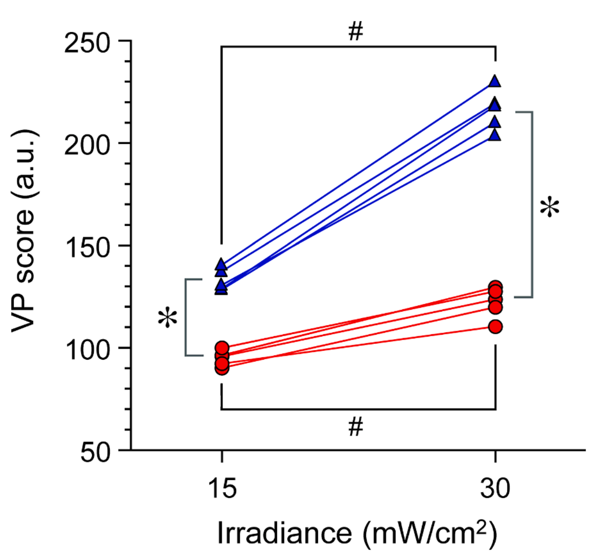

Fig. 5. Graph showing visibility performance (VP) score of the Foley-NIRC catheter (red filled circles) and HICARL catheter (blue filled triangles) during weak (15 mW/cm^2) and strong (30 mW/cm^2) irradiation of excitation light. $^*p < 0.05$, $n = 5$ for each group; $^{\#}p < 0.05$, $n = 5$ for paired samples. a.u., arbitrary units.

of the Foley catheter seem to be highly needed in clinical practice. Our NIR fluorescent Foley catheter, which has the same structure and implantation method as a conventional Foley catheter, would be an easy-to-use tool for visualizing the urethra during image-guided surgery of lower rectal cancer.

The bench performance tests revealed that the Foley-NIRC catheter and HICARL catheter emitted 3.42 and 6.43 times more fluorescence than the Foley-ICG catheter, respectively. In a recent quantitative study, Barberio et al. demonstrated that a Foley catheter coated with NIR fluorescent acrylic resin, which emitted NIR fluorescence four times brighter than the Foley-ICG catheter, can accurately guide the location of the urethra in cadavers [16]. Based on their findings, the HICARL catheter is also expected to guide the location of the urethra by its NIR fluorescence, while the Foley-NIRC catheter would be less promising.

As expected from the results of the bench performance tests, the location of the HICARL catheter placed in the anorectum with a wall thickness of approximately 4 mm was clearly delineated in its entirety by NIR fluorescence, whereas that of the Foley-NIRC catheter was faintly or only partially visible. The required performance for a Foley catheter to locate the urethra would be to emit NIR fluorescence that is at least four times brighter than that of the Foley-ICG catheter. To our knowledge, this is the first report of a medical-grade Foley catheter that is made of silicone rubber with sufficient NIR fluorescence intensity for intraoperative urethral visualization.

While the present study demonstrated feasibility of our NIR fluorescent Foley catheter, there remains to be done in the future. Clinical tests are required to confirm its efficacy. Although we used our custom-made laparoscopic system for the visibility performance assessment, differences in visibility of the HICARL catheter between models of commercially available laparoscopic systems should be investigated prior to clinical studies.

In conclusions, a newly developed HICARL catheter, which has the same structure and implantation method as a conventional Foley catheter, emits NIR fluorescence that is more than four times brighter than that of the Foley-ICG catheter. Therefore, the HICARL catheter is a promising and easy-to-use tool to prevent urethral injury during NIR fluorescence-guided surgery of lower rectal cancer.

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CRediT authorship contribution statement

Takayuki Sato: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Ichiro Kitani:** Writing – review & editing, Validation, Resources, Project administration, Investigation.

Declaration of competing interest

Takayuki Sato and Ichiro Kitani have no conflict of interest to disclose.

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