Comparison Between 5-Aminolevulinic Acid Photodynamic Diagnosis and Narrow- Band Imaging for Bladder Cancer Detection: A Single-Center Retrospective Cohort Study

Hiroki Hagimoto (hiroki1104hagimoto@gmail.com)
Kobe City Medical Center General Hospital
Noriyuki Makita
Kobe City Medical Center General Hospital
Yuta Mine
Kobe City Medical Center General Hospital
Hidetoshi Kokubun
Kobe City Medical Center General Hospital
Shiori Murata
Kobe City Medical Center General Hospital
Yohei Abe
Kobe City Medical Center General Hospital
Masashi Kubota
Kobe City Medical Center General Hospital
Naofumi Tsutsumi
Kobe City Medical Center General Hospital
Toshinari Yamasaki
Kobe City Medical Center General Hospital
Mutsushi Kawakita
Kobe City Medical Center General Hospital

Research Article

Keywords: bladder cancer, 5-aminolevulinic acid, narrow-band imaging, photodynamic diagnosis, transurethral resection of bladder tumor

Posted Date: August 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-767864/v1

Abstract

Background

No comparative studies exist between 5-aminolevulinic acid-photodynamic diagnosis (PDD) and narrow-band imaging (NBI) for the detection of urothelial carcinoma. Therefore, we compared 5-aminolevulinic acid-mediated PDD with NBI for cancer detection during transurethral resection of bladder tumors.

Methods

Between June 2018 and October 2020, 114 patients and 282 lesions were included in the analysis. Patients were orally administered 5-aminolevulinic acid (20 mg/kg) 2 h before transurethral resection of bladder tumors. The bladder was inspected with white light, PDD, and NBI for each patient and all areas that were positive by at least one method were resected or biopsied. The imaging data were then compared to the pathology results.

Results

The sensitivity, specificity, positive predictive value, and negative predictive value for detecting urothelial carcinoma were 88.1%, 47.5%, 80.9%, and 61.3% for white light; 89.6%, 22.5%, 74.5%, and 46.2% for PDD; and 76.2%, 46.3%, 78.2%, and 43.5% for NBI, respectively. PPD was significantly more sensitive than NBI for all lesions ($p<0.001$), including carcinoma *in situ* lesions (94.6% vs. 54.1%, $p<0.001$).

Conclusions

PDD can increase the detection rate of bladder cancer compared to NBI by greater than 10%. Adding PDD to white light can detect 100% of carcinoma *in situ* lesions.

Background

Bladder cancer is the ninth most frequently diagnosed malignancy in the world [1] and is the fourth leading cause of death among men [2]. The 5-year recurrence rate of non-muscle-invasive bladder cancer ranges from 50–70%, and the reported 5-year progression rate ranges from 10–30% [3].Transurethral resection of bladder tumor (TURBT) with intraoperative detection of the cancer by white light (WL) is the standard treatment for non-muscle invasive bladder cancer [4]. However, it is difficult to detect flat lesions, including carcinoma *in situ* (CIS), with WL alone, and the high rate of intravesical recurrence of CIS is problematic. Therefore, it is important to accurately detect CIS in order to be able to remove any residual tumor. It is known that the addition of photodynamic diagnosis (PDD) and narrow-band imaging (NBI) to WL increases the detection rate of cancer in flat lesions that do not appear as distinct lesions with conventional WL [5–8]. PDD and NBI are also associated with lower recurrence rates compared to WL only [2, 9–11]. PDD is a technique that exploits the property of tumors or rapidly proliferating cells to emit red fluorescence during cystoscopy using blue light, after oral or intravesical administration of a photosensitizing precursor such as 5-aminolevulinic acid (5-ALA). NBI is a technique that utilizes the fact that tissue penetration by light depends on its wavelength. By exposing the bladder wall to light with two narrow-banded wavelengths, which are easily absorbed by hemoglobin, capillaries on the surface of the mucosa are displayed as brown and blood vessels inside the submucosa as blue-green, highlighting the tumor. PDD using 5-ALA (5-ALA-PDD) for non-muscle invasive bladder cancer reduces the risk of recurrence [12] and has a real-world sensitivity and specificity of 90.1% and 61.2%, respectively [13]. For NBI, a meta-analysis showed that the pooled sensitivity and specificity for non-muscle invasive bladder cancer were 94.8% and 65.6%, respectively [14].

The 2021 European Association of Urology guidelines strongly recommend taking biopsies from both abnormal-looking urothelium and normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior, and posterior bladder wall) when cytology is positive, in case of a history of high grade tumors, and for tumors with non-papillary appearance. Moreover, PDD-guided biopsies should be used if equipment is available. However, bladder biopsy using NBI during TURBT is weakly recommended [15].

Some studies have examined the usefulness of combining PPD and NBI for the detection of flat lesions [16, 17]. However, no comparative studies exist between 5-ALA-PPD and NBI for the detection of urothelial carcinoma, including both protruded and flat lesions. The purpose of this study was to compare 5-ALA-PDD and NBI in terms of bladder cancer detection capability in the same patients.

Methods

Study cohort and design

This single-center retrospective cohort study was approved by the appropriate institutional review board (IRB No. zn210416) and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). All patients were informed of the efficacy and adverse events associated with 5-ALA-PDD and NBI and we obtained written informed consent from all patients before the operations. The purpose of this study is to determine whether 5-ALA-PDD or NBI is superior in detecting bladder cancer during TURBT. A total of 141 patients with primary bladder cancer who underwent 5-ALA-PDD and NBI-assisted TURBT between June 2018 and October 2020 were included in the study. Eighteen patients with random bladder biopsies; five patients with histology consistent with prostate cancer, squamous cell carcinoma, or renal cell carcinoma; and four patients with no observation records for either NBI or 5-ALA-PDD were excluded. Included in the analysis were 114 patients with 282 lesions. Figure 1 shows the flow diagram of the study.

Surgical procedure

All patients were orally administered 20 mg/kg of 5-ALA 2 h before the start of surgery. In all cases, the positive and negative lesions were determined by two urologists. At the time of TURBT, the bladder was inspected with WL, 5-ALA-PDD, and NBI, and all lesions deemed positive by at least one modality were resected. WL was used first and was followed by either 5-ALA-PDD or NBI depending on the surgeon's preference. We used an AUTOCON® III 400 (KARL STORZ, Tuttlingen, Germany) for PDD and an OES ELITE 30° optic tube 4 mm (Olympus, Tokyo, Japan) for NBI. Bladder inspection with each modality occurred consecutively. Figure 2 shows a typical view by each modality. After TURBT, 50 mg of epirubicin hydrochloride in 50 mL of saline solution was instilled into the bladder through a Foley catheter, which was clamped for 30 min. The patients were kept out of direct sunlight for 48 h after surgery. We reviewed the pathology results and the intraoperative detection frequencies of each modality, and, accordingly, determined the cancer detection rate and sensitivity for each modality. Grading was performed according to the 2016 World Health Organization classification [18].

Safety assessment

We noted the incidence of side effects common with 5-ALA, such as vomiting, liver damage, and hypotension. Gradings were based on the Clavien-Dindo classification scheme [19].

Statistical analysis

The extracted data from the prospective database included age, sex, body mass index, preoperative urine cytology, operation time, surgeon, anesthetic method, pathological examination, length of hospital stay, readmission, in-hospital complications, and Clavien-Dindo grade. We calculated and compared the sensitivity, specificity, positive predictive value, and negative predictive value for each lesion. Significant differences between the two groups were assessed based on McNemar's odds ratio using standard analysis software (BellCurve for Excel; Social Survey Research Information Co., Ltd., Tokyo, Japan). All statistical tests were two-tailed, with $p < 0.05$ indicating statistical significance.

Results

In total, 282 lesions from 114 patients were included in the study, and all of them were available for data analysis. Table 1 shows the patients' characteristics. The specimen histology is presented in Table 2. Urothelial carcinoma (UC) was diagnosed in 202 specimens, whereas the remaining 80 were benign. Of the benign specimens, 3 were consistent with dysplasia, 13 with papilloma, and the rest were normal tissues. Table 3 shows the sensitivity of each modality for the detection of UC and the specificity for benign lesions. As shown, 5-ALA-PDD had a higher overall sensitivity than NBI (89.6% vs. 76.2%, $p < 0.001$). It also was more sensitive than NBI for CIS lesions (94.6% vs. 54.1%, $p < 0.001$). We were able to detect 100% of the CIS lesions with combined WL and PDD, thus increasing the rate of detection by 35.1% compared with that of WL alone.

Adverse events, including hypotension (N = 61), elevated liver enzyme levels (N = 6), and vomiting (N = 20), were of less than grade 3 Clavien-Dindo classification. The patients who experienced vomiting did so within a median of 5.9 (IQR: 1.3–7.4) hours after 5-ALA administration. In all cases, nausea disappeared by the next day. All incidents (N = 61) of hypotension were of grade 2 or lower. Of the 67 patients who received lumbar anesthesia, 22 patients (32.8%) received intraoperative vasopressors, and of the 47 patients who received general anesthesia, 39 patients (83.0%) received vasopressors during induction. None of the patients required vasopressors after surgery. Regarding postoperative complications, there were 12 cases of grade 1 or higher as per the Clavien-Dindo classification. There was only one case of grade 3a, which required endoscopic retrograde cholangiopancreatography for fever due to postoperative recurrence of hepatocellular carcinoma. The remaining 11 cases were below grade 2, such as temporary postoperative urinary retention and bladder tamponade.

Discussion

In this study, 5-ALA-PDD was superior and considered more useful than NBI in reducing the number of missed tumors. The detection rate of pTis lesions in the WL and PDD group was 100%, and the rate of additionally detected CIS with WL and PDD was increased by 35.1% compared with WL alone. This proved that 5-ALA-PDD is particularly useful in detecting flat lesions, such as CIS. The present study determined a lower specificity for PDD than other reports [12, 13]. This may have occurred because of the exclusion of cases with random biopsies, such as cold-cup biopsies of normal-looking lesions.

According to the literature, transient elevation of liver enzymes of grade 3 or lower, as well as hypotension, can occur due to 5-ALA, and caution is recommended with its use [20, 21]. In this study, there was only one case of grade 3a adverse effects, which was not associated with 5-ALA. Moreover, the rest of the adverse events were grade 2 or lower and could be easily managed.

The present study has several limitations which are as follows: 1) the small number of patients included, 2) single-center retrospective design, 3) inter-observer and intra-observer bias (due to the subjective nature of visual estimation and could be potentially overcome by the development of methods to quantify visual information), and 4) procedure bias introduced by the order of use of each modality and the time between 5-ALA administration and bladder inspection in PDD. There is also a phenomenon called photobleaching, wherein 5-ALA degrades upon repeated illumination causing reduced detection rate [22]. Although observation at 2–4 h after 5-ALA oral administration is recommended, the time of 5-ALA exposure to light may be less important, as it has been shown that no significant difference exists between exposure times of 2–3 h and 4 hours or more [9]. Recent studies have shown a fluorescence enhancement effect using polyethylene glycol-modified titanium dioxide nanoparticles [22]. This may be useful for reducing the bias caused by photobleaching.

Conclusions

5-ALA-PDD at the time of TURBT increased the detection rate of bladder cancer, especially of flat lesions such as CIS, compared to NBI. Furthermore, the combination of PDD with WL, the current standard of care, achieves 100% sensitivity in the detection of CIS; however, prospective studies are needed to verify these results.

Abbreviations

5-ALA: 5-aminolevulinic acid

CIS: carcinoma in situ

NBI: narrow-band imaging

PDD: photodynamic diagnosis

TURBT: transurethral resection of bladder tumor

WL: white light

WN: white light with NBI

Declarations

Ethics approval and consent to participate

This single-center retrospective cohort study was approved by the institutional review board (IRB No. zn210416) and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). All patients were informed of the efficacy and adverse events associated with 5-ALA-PDD and NBI and we obtained written informed consent from all patients before the operations.

Consent for publication

All patients signed informed consent regarding publishing their data and photographs.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors performed the surgeries and records as surgeons after providing explanations to the patients. They also read and approved the final manuscript.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

References

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol. 2017; doi:10.1016/j.eururo.2016.06.010.
2. Lenis AT, Lec PM, Chamie K, MSHS, MD, Mshs MD. Bladder cancer: a review. JAMA. 2020; doi:10.1001/jama.2020.17598.
3. Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström PU, Choi W, et al. Bladder cancer. Lancet. 2016; doi:10.1016/s0140-6736(16)30512-8.
4. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017; doi:10.1016/j.eururo.2016.05.041.
5. Kriegmair M, Baumgartner R, Knüchel R, Stepp H, Hofstädter F, Hofstetter A. Detection of early bladder cancer by 5-aminolevulinic acid induced porphyrin fluorescence. J Urol. 1996;155:105–9;discussion 109 – 10.
6. Filbeck T, Roessler W, Knuechel R, Straub M, Kiel HJ, Wieland WF. Clinical results of the transurethreal resection and evaluation of superficial bladder carcinomas by means of fluorescence diagnosis after intravesical instillation of 5-aminolevulinic acid. J Endourol. 1999; doi:10.1089/end.1999.13.117.
7. De Dominicis C, Liberti M, Perugia G, De Nunzio C, Sciobica F, Zuccalà A, et al. Role of 5-aminolevulinic acid in the diagnosis and treatment of superficial bladder cancer: improvement in diagnostic sensitivity. Urology. 2001; doi:10.1016/s0090-4295(01)00948-7.
8. Zaak D, Kriegmair M, Stepp H, Stepp H, Baumgartner R, Oberneder R, et al. Endoscopic detection of transitional cell carcinoma with 5-aminolevulinic acid: results of 1012 fluorescence endoscopies. Urology. 2001; doi:10.1016/s0090-4295(00)01053-0.
9. Naselli A, Introini C, Timossi L, Spina B, Fontana V, Pezzi R, et al. A randomized prospective trial to assess the impact of transurethral resection in narrow band imaging modality on non-muscle-invasive bladder cancer recurrence. Eur Urol. 2012. doi:10.1016/j.eururo.2012.01.018.
10. Kutwin P, Konecki T, Cichocki M, Falkowski P, Jabłonowski Z. Photodynamic diagnosis and narrow-band imaging in the management of bladder cancer: a review. Photomed Laser Surg. 2017; doi:10.1089/pho.2016.4217.
11. Grossman HB, Stenzl A, Fradet Y, Mynderse LA, Kriegmair M, Witjes JA, et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. J Urol. 2012; doi:10.1016/j.juro.2012.03.007.
12. Nakai Y, Inoue K, Tsuzuki T, Shimamoto T, Shuin T, Nagao K, et al. Oral 5-aminolevulinic acid-mediated photodynamic diagnosis using fluorescence cystoscopy for non-muscle-invasive bladder cancer: a multicenter phase III study. Int J Urol. 2018; doi:10.1111/iju.13718.

13. Yamamoto S, Fukuhara H, Karashima T, Inoue K. Real-world experience with 5-aminolevulinic acid for the photodynamic diagnosis of bladder cancer: diagnostic accuracy and safety. Photodiagnosis Photodyn Ther. 2020; doi:10.1016/j.pdpdt.2020.101999.
14. Xiong Y, Li J, Ma S, Ge J, Zhou L, Li D, et al. A meta-analysis of narrow band imaging for the diagnosis and therapeutic outcome of non-muscle invasive bladder cancer. PLOS ONE. 2017; doi:10.1371/journal.pone.0170819.
15. Babjuk M, Burger M, Comperat E, Gontero P, Liedberg F, Masson-Lecomte AH, et al. EAU guidelines on non-muscle-invasive bladder cancer. European Association of Urology. 2021. https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/. Accessed 27 July 2021.
16. Naya Y, Oishi M, Yamada Y, Ueda T, Fujihara A, Nakanishi H, et al. Initial experience of combined use of photodynamic diagnosis and narrow band imaging for detection of flat urothelial lesion. Int J Clin Oncol. 2015; doi:10.1007/s10147-014-0748-5.
17. Drejer D, Béji S, Oezeke R, Nielsen AM, Høyer S, Bjerklund Johansen TE, et al. Comparison of white light, photodynamic diagnosis, and narrow-band imaging in detection of carcinoma in situ or flat dysplasia at transurethral resection of the bladder: the DaBlaCa-8 study. Urology. 2017; doi:10.1016/j.urology.2016.11.032.
18. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter V. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. Eur Urol. 2016. doi: https://doi.org/10.1016/j.eururo.2016.02.028
19. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; doi: 10.1097/SLA.0b013e3181b13ca2.
20. Yatabe T, Marie SL, Fukuhara H, Karashima T, Inoue K, Yokoyama M. 5-aminolevulinic acid-induced severe hypotension during transurethral resection of a bladder tumor: A case report. JA Clin Rep. 2019; doi:10.1186/s40981-019-0279-1.
21. Nohara T, Kato Y, Nakano T, Nakagawa T, Iwamoto H, Yaegashi H, et al. Intraoperative hypotension caused by oral administration of 5-aminolevulinic acid for photodynamic diagnosis in patients with bladder cancer. Int J Urol. 2019; doi: 10.1111/iju.14099.
22. Kanehira K, Yano Y, Hasumi H, Fukuhara H, Inoue K, Hanazaki K, et al. Fluorescence enhancement effect of TiO2 nanoparticles and application for photodynamic diagnosis. Int J Mol Sci. 2019; doi:10.3390/ijms20153698.

Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

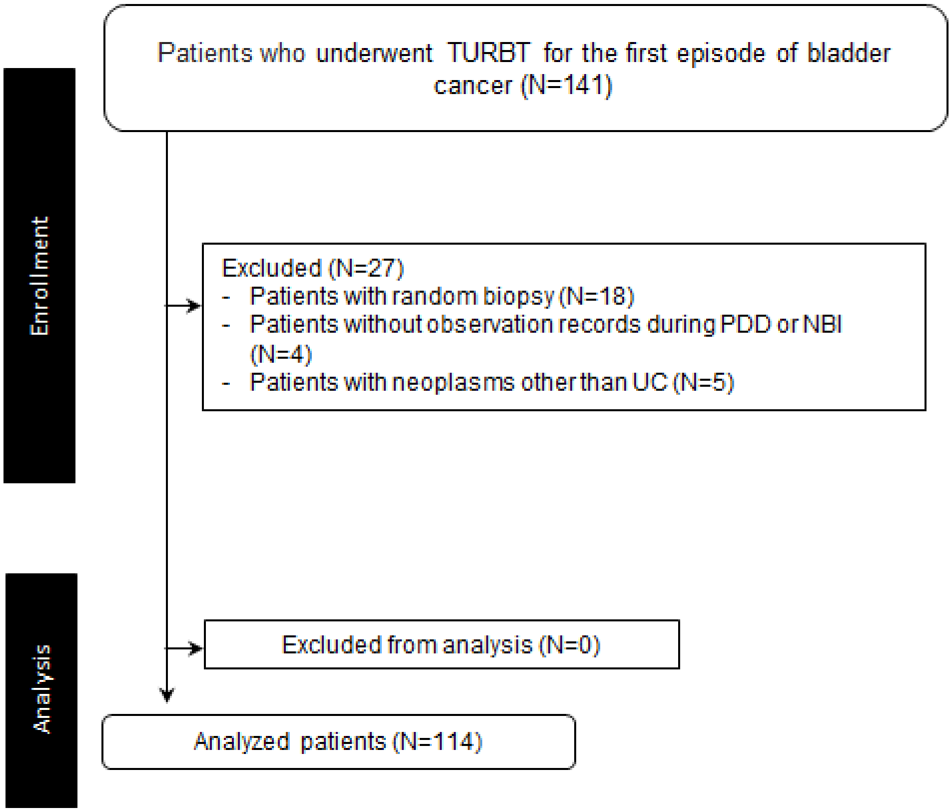

Figure 1

Flow diagram of patient enrollment NBI, narrow-band imaging; PDD, photodynamic diagnosis; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma

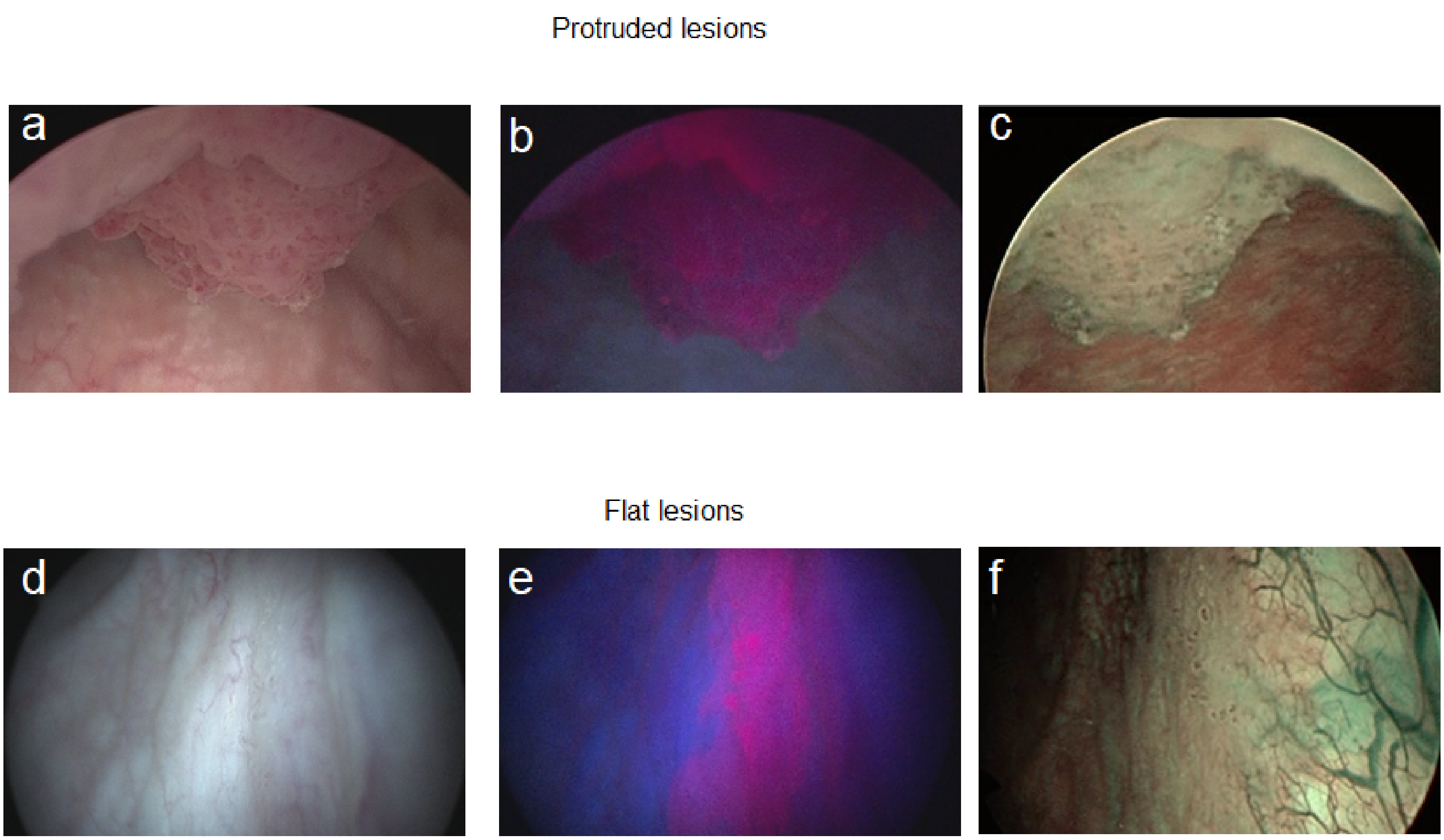

Figure 2

Representative endoscopy images Legends: Positive tumor findings in protruded lesions using (a) WL, (b) PDD, (c) NBI and in flat lesions using (d) WL, (e) PDD, (f) NBI NBI, narrow-band imaging; PDD, photodynamic diagnosis; WL, white light

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table01.png
- Table02.png
- Table03.png