Photodynamic Diagnosis of Peritoneal Dissemination of Colorectal Cancer Using 5-Aminolevulinic Acid during Laparoscopic Surgery

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Photodynamic Diagnosis of Peritoneal Dissemination of Colorectal Cancer Using 5-Aminolevulinic Acid during Laparoscopic Surgery

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Background: Photodynamic diagnosis (PDD) using 5-aminolevulinic acid (5-ALA) is useful for detecting microperitoneal dissemination in gastric cancer. However, reports on its use in colorectal cancer are sparse. In this study, we performed PDD with 5-ALA to diagnose peritoneal dissemination in colorectal cancer during laparoscopic surgery.

Methods: Between January 2018 and March 2019, we examined six patients scheduled laparoscopic surgery for colorectal cancer (cT3 or deeper) with suspected peritoneal dissemination. A solution of 5-ALA (20 mg/kg) in water was orally administered 3 to 4 hours before surgery. Intraoperatively, the peritoneal cavity was observed with white and fluorescent lights. Nodules suspected as dissemination lesions were resected and the presence or absence of seeding was confirmed histopathologically.

Results: The median time from oral 5-ALA administration to observation was 226 minutes. Peritoneal nodules found in four of six cases using white light were collected. In Case 5, white nodules were observed in white light and luminescence in fluorescent light. Of the nodules collected, only that of Case 5 was pathologically diagnosed as disseminating. No adverse events were observed.

Conclusions: We attempted PDD using 5-ALA during laparoscopic surgery for colorectal cancer. Observing more cases and optimizing observation conditions are required to improve accuracy.

This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN Exam ID: UMIN000030531).

Keywords: 5-aminolevulinic acid, dissemination, photodynamic diagnosis, colorectal cancer

Introduction

In digestive cancers, especially gastric cancer, peritoneal dissemination is actively diagnosed by laparoscopic examination and peritoneal lavage cytology. Colorectal cancer, in contrast, has fewer cases of peritoneal dissemination than gastric cancer, and the significance of the ascites fluid cytology is unclear. Positive peritoneal dissemination (P+) is a poor prognostic factor for colorectal cancer. The remarkable advancement of chemotherapy

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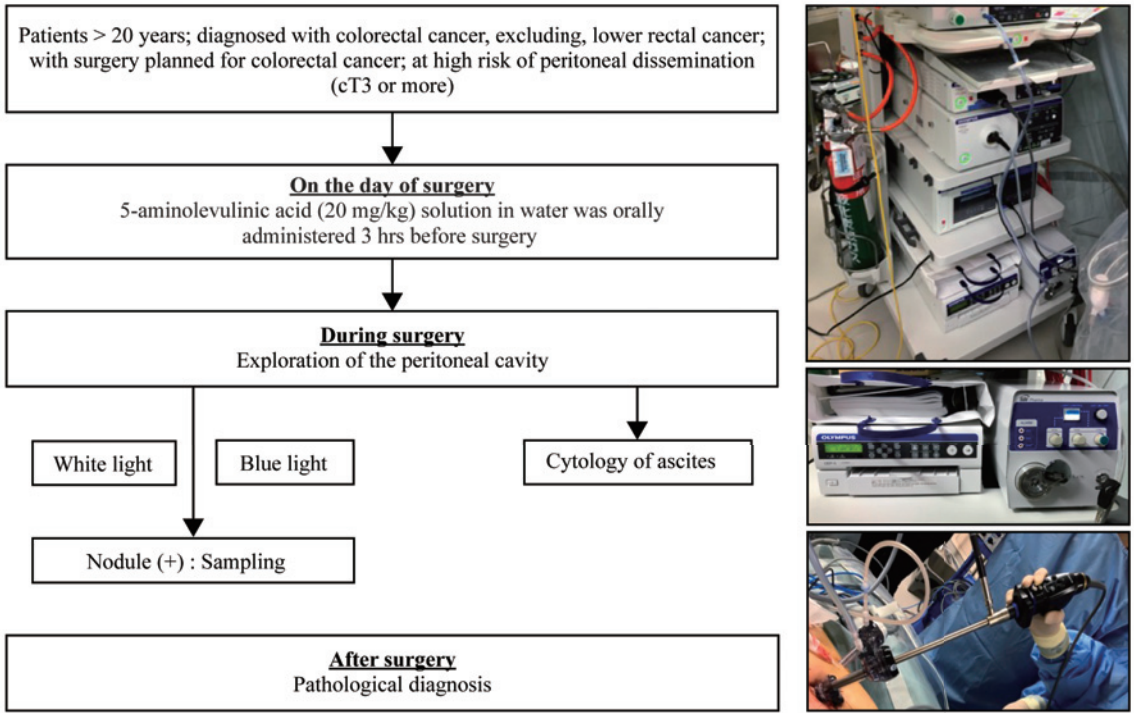

Figure 1. Study design.

and the use of appropriate surgeries in recent years have facilitated the prolongation of prognosis even in cases with peritoneal dissemination.[1-5] However, it is difficult to diagnose minute peritoneal dissemination before and during surgery. Even if a disseminated nodule is identified during surgery, it is difficult to determine if it is peritoneal.

5-aminolevulinic acid (5-ALA) is useful for detecting microperitoneal dissemination of gastric cancer that cannot be detected by diagnostic imaging or ascites fluid cytology.[6-8] A multicenter joint study in 2007 focused on the detection of peritoneal dissemination of gastric cancer by laparoscopic examination using 5-ALA.[9] A study by Kondo et al.[10] detected peritoneal dissemination of colorectal cancer by laparoscopic examination using 5-ALA; however, the accuracy is questionable due to the small number of cases included (n=12). Therefore, the prospect of performing 5-ALA photodynamic diagnosis (PDD) during laparoscopic surgery of colorectal cancer is unresolved. In this study, we aimed to examine the feasibility of using PDD during laparoscopic surgery of colorectal cancer.

Materials and Methods

This study is a single-center, unblinded, exploratory trial (UMIN Exam ID: 000030531). This study was approved by the Tokyo Women's Medical University Hospital Ethics Committee (Approval No. 170401).

1. Subjects

We examined patients aged 20 years and above with colorectal cancer, excluding lower rectal cancer, who were suspected of having peritoneal dissemination, such as perforation, or had a tumor depth of cT3 or deeper and were scheduled to undergo laparoscopic surgery. We observed 6 patients, who provided consent, between January 2018 and March 2019.

2. Method

On the day of surgery, a solution of 5-ALA hydrochloride (20 mg/kg) in water was administered orally to the patient at least 3 hours before admission to the operating room. Once the surgery commenced, the presence or absence of dissemination was first observed laparoscopically with white light (normal light source), and then with blue fluorescent light. The doctors participating in the surgery (surgeon, assistant, and camera operator) dis-

cuss and judge whether the fluorescence emission was positive or negative. Nodules suspected as being dissemination lesions were sampled and evaluated histopathologically. In addition, the ascitic fluid was collected during the operation to confirm the presence or absence of malignancy. After the initial procedures, the surgery was performed as usual. The research protocol is shown in **Figure 1**.

Endpoints of this study were changes in the following items before and after treatment: (1) the occurrence of adverse events with the use of 5-ALA, (2) the occurrence of adverse events with the use of the fluorescent light source, (3) intraoperative gross diagnosis of dissemination, diagnosis of dissemination under fluorescence, ascites fluid cytology, and differences in pathological diagnosis, (4) sensitivity, and (5) specificity of fluorescence.

Patients with porphyria and photosensitivity were excluded from the study because their symptoms may worsen; however, all cases were shielded from light with a curtain for several days after surgery.

3. 5-Aminolevulinic acid hydrochloride

5-ALA hydrochloride follows the heme biosynthetic pathway as the in vivo 5-ALA. Heme is generated via protoporphyrin IX (PPIX); PPIX when excited by blue light (400 to 410 nm) emits red fluorescence. In malignant tumor cells, the enzyme activity is higher during PPIX production and lower during the breakdown of PPIX to form heme compared to normal cells. Therefore, a large amount of PPIX accumulates in tumor cells. This property has been widely used in the field of neurosurgery for visualizing tumor tissues during tumor resections of malignant glioma and it is covered by the national health insurance system in Japan.

ALAGLIO® internal preparation 1.5 g (SBI Pharma Co., Ltd., Germany) is the most desirable and originally approved drug for malignant glioma. The manufacturing capacity of the company was limited, and hence, the drug was prioritized for using to treat glioma, its indications, and bladder cancer. It was recommended to limit its use for unapproved indications. Therefore, as a substitute, we were provided with an original for "ALAGLIO® internal preparation 1.5 g" (quality equivalent to that of Japanese and German originals) that meets the same standards, was pharmaceutically equivalent, and manufactured in compliance with good manufacturing practice (GMP). We reported to the Pharmaceutical Food Monitoring and Guidance/Drug Countermeasures Division of the Ministry of Health, Labor and Welfare that confirmed that unapproved drugs may be provided by pharmaceutical companies for clinical research. We applied to the Tokyo Women's Medical University Hospital Unapproved/Contraindicated/Off-label Drug Evaluation Office for permission and obtained approval.

In a domestic clinical study of "ALAGLIO® internal preparation 1.5 g" in bladder cancer patients, adverse drug reactions were observed in 46 (37.4%) of 123 cases who were recruited for drug safety evaluation. Aspartate aminotransferase (AST) increased in 21 cases (17.1%), alanine aminotransferase (ALT) in 17 (13.8%), lactate dehydrogenase (LDH) in 12 (9.8%), blood bilirubin in 12 (9.8%), and γ-glutamyl transpeptidase (γ-GTP) in 10 (8.1%); nausea and vomiting were seen in 9 (7.3%) and 8 cases (6.5%), respectively.[11]

4. Test equipment, light source equipment

Olympus Medical Systems equipment (VISERA ELITE video system center: OLYMPUS OTV-S190, VISERA video system center camera head: OLYMPUS OTV-S7, OLYMPUS laparoscope: WA50373B, VISERA ELITE high-intensity light source device: OLYMPUS CLV-S190, high-resolution LCD monitor: OEV-261H) was used. The commercially available light sources for rigid scope capable of being used for PDD with 5-ALA include Karl Storz's PDD system and SBI Pharma Co., Ltd. Aladuck®. In our study, Aladuck® LS-D LED was connected as a light source for fluorescence observation because of its compatibility with the Olympus rigid scope used in our department. Aladuck® has been approved by the regulatory affairs department as a class 1 medical device, and its safety is guaranteed.

Laparoscopic devices and laparoscopes were used for laparoscopic surgery, and their safety has been proved over time.

Results

1. Patient background (Table 1)

One male and five female patients were included in the

Table 1. Clinical characteristics of the patients.

Case	Age	Sex	Location	Clinical diagnosis					
				Tumor depth	Stage	Dissemination	Distant metastasis	Symptomatic obstruction	Perforation
1	46	F	RS	SI (uterus)	IIIB	(+)	(-)	(+): ileus tube, transanal decompression tube	(-)
1’	47	F	RS	SS	IIIB	(-)	(-)	(-)	(-)
2	43	F	Appendix	SM	I	(-)	(-)	(-)	(+)
3	49	F	S	SI (ileum)	IIIA	(-)	(-)	(+)	(-)
4	68	F	S	SE	IVA	(-)	M1a (PUL1)	(+): SEMS*	(-)
5	60	M	A	SE	IVC	(+)	M1c2 (H3, P3)	(+): SEMS*	(+)

a) *SEMS, self-expanded metallic stent.

b) Case 1 and 1’ denote the same patient.

Neo-adjuvant chemotherapy was performed after a laparoscopic transverse colostomy (the first surgery).

Laparoscopic anterior resection was performed after adjuvant chemotherapy (the second surgery).

c) Case 2 is a patient on whom additional resection after appendectomy for perforated appendicitis.

Table 2. Results of the intraoperative observation, pathological diagnosis and prognosis of patients.

Case	Time from oral administration to observation (min)	White light		Fluorescence		Pathology				Adverse events	Prognosis	Observation period (days)
		Peritoneal nodule		Peritoneal nodule	Tumor***	Tumor depth	Tumor differentiation	Dissemination	Ascites fluid cytology			
1	296	(+)		(-)	N/A****	-	-	(-)	V	(-)	RFS*	902
1’	230	(+)		(-)	(-)	serosa	tub2	(-)	II	(-)	RFS*	794
2	215	(+)		(-)	(-)	submucosa	(tub1)	(-)	I	(-)	RFS*	962
3	221	(-)		(-)	(+)	subserosa	tub2	(-)	II	(-)	RFS*	561
4	281	(-)		(-)	(+)	subserosa	tub2>tub1	(-)	N/A****	(-)	CBS**	155
5	97	#1 (mesentery)	(+)	(+)	N/A****	serosa	well (tub1>tub2)	(+)	N/A****	(-)	CBS**	575
		#2 (peritoneum)	(+)	(+)				(-)				
		#3 (peritoneum)	(+)	(-)				(-)				

a) *RFS, recurrence-free survival.

b) **CBS, cancer-bearing survival.

c) *** Tumor: fluorescence observation of the main tumor from the mucosal side.

d) **** N/A, not applicable.

study. The tumor was localized in the appendix in one patient, ascending colon in one, sigmoid colon in two, and rectum in two. The clinical T (the depth of invasion) was T1b in one case (the case of appendix cancer, additional resection after appendectomy was performed for perforated appendicitis), T4a in four, and T4b in one. The clinical stage was Stage I in one, IIIa in one, IIIb in two, IVA in one and IVC in one. Dissemination was suspected based on preoperative diagnostic imaging in one case (Case 5). In four cases, decompression for intestinal obstruction was required before surgery (two stents and two transanal decompression tubes).

In case 4, colectomy was performed with a clinical diagnosis of sigmoid colon cancer and simultaneous lung metastasis. Partial lung resection was performed 43 days after the operation, and a histopathological diagnosis of small cell carcinoma was made, and it was found that the cancer was double cancer.

2. Major findings (Table 2)

The median time from the administration of oral 5-ALA to observation was 226 (97-296) minutes. Peritoneal nodules were detected in four of six cases using white light and were collected. In Case 5, a large number of white nodules were observed in the abdominal cavity, and fluorescence observation revealed a mild red emission fluorescence. The nodule in Case 5 was macroscopically suspected as a peritoneal dissemination lesion and was pathologically diagnosed as dissemination. No new lesions were detected by fluorescence light. Case 5 was

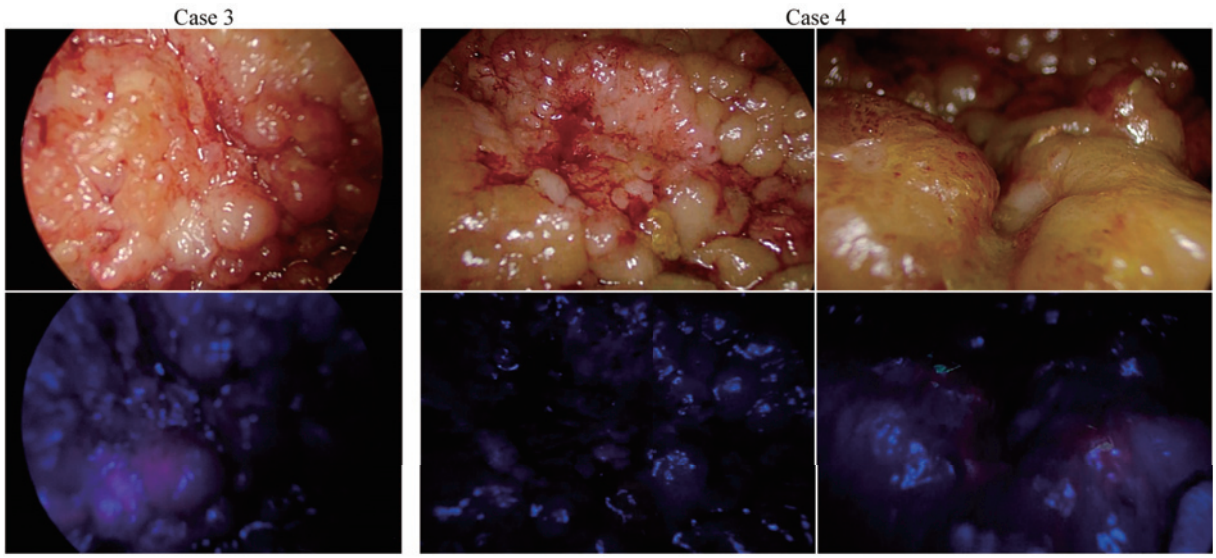

Figure 2. Fluorescence observation of the resected specimens.
Fluorescence observation of the main tumor from the mucosal side revealed red luminescence after removal. Proximity to the tumor helped detect the luminescence.

the only case that had peritoneal dissemination.

The median observation period was 684.5 (155-902) days. There were four cases of recurrence-free survival and two cases of cancer-bearing survival. Of the two cancer-bearing survivors, one was diagnosed with dissemination preoperatively and the other had two cancers (small-cell lung and colorectal cancers). There were no new metastatic recurrences.

No adverse events related to 5-ALA, such as hypotension and photosensitivity, were observed after the induction of anesthesia.

The observation of specimens from Cases 3 and 4 are shown in **Figure 2**, and Case 5 is shown in **Figure 3**.

3. Endpoints

In this study, no adverse events related to 5-ALA or the fluorescent light source were observed. Finally, six nodules suspected as being dissemination lesions were sampled and evaluated histopathologically. Two nodules from Case 5 showed luminescence by fluorescence observation, and one of them was pathologically proven to be disseminated, but the other was fibrosis. The pathological diagnosis of five nodules that were not disseminated were fibrosis, leiomyoma, mature adipocytes, and endometriosis. In particular, in Case 5, three nodules suspected to be disseminated were collected from a large number of nodules, but two nodules (**Figure 3**, #2, #3) were diagnosed as dense fibrosis pathologically. It revealed the limit and difficulty of intraoperative diagnosis of dissemination. Sensitivity and specificity of fluorescence observation: Sensitivity was 50% and specificity was 80% in this study.

Discussion

Simultaneous peritoneal dissemination of colorectal cancer is generally less frequent than gastric and pancreatic cancers, and is said to account for about 4.5% in all colorectal cancers.[2] For gastric and pancreatic cancers, the presence or absence of dissemination has a great influence on the selection of an appropriate surgical method. However, for colorectal cancer, primary lesion resection is often performed to control bleeding and stenosis, regardless of dissemination. Due to the advances in chemotherapy and radiotherapy, if resection is not excessively invasive as in P1 and P2 (localized metastasis),[12] simultaneous primary lesion resection is strongly recommended by the regulations for colorectal cancer handling.[13] Therefore, it is important to determine the presence or absence of dissemination. Preoperative peritoneal dissemination is diagnosed by CT or PET-CT. FDG-PET is excellent in detecting malignant tumors; however, PET alone may not be able to detect lesions of 1 cm or less. It is, therefore, used in combination with MDCT and MRI as a

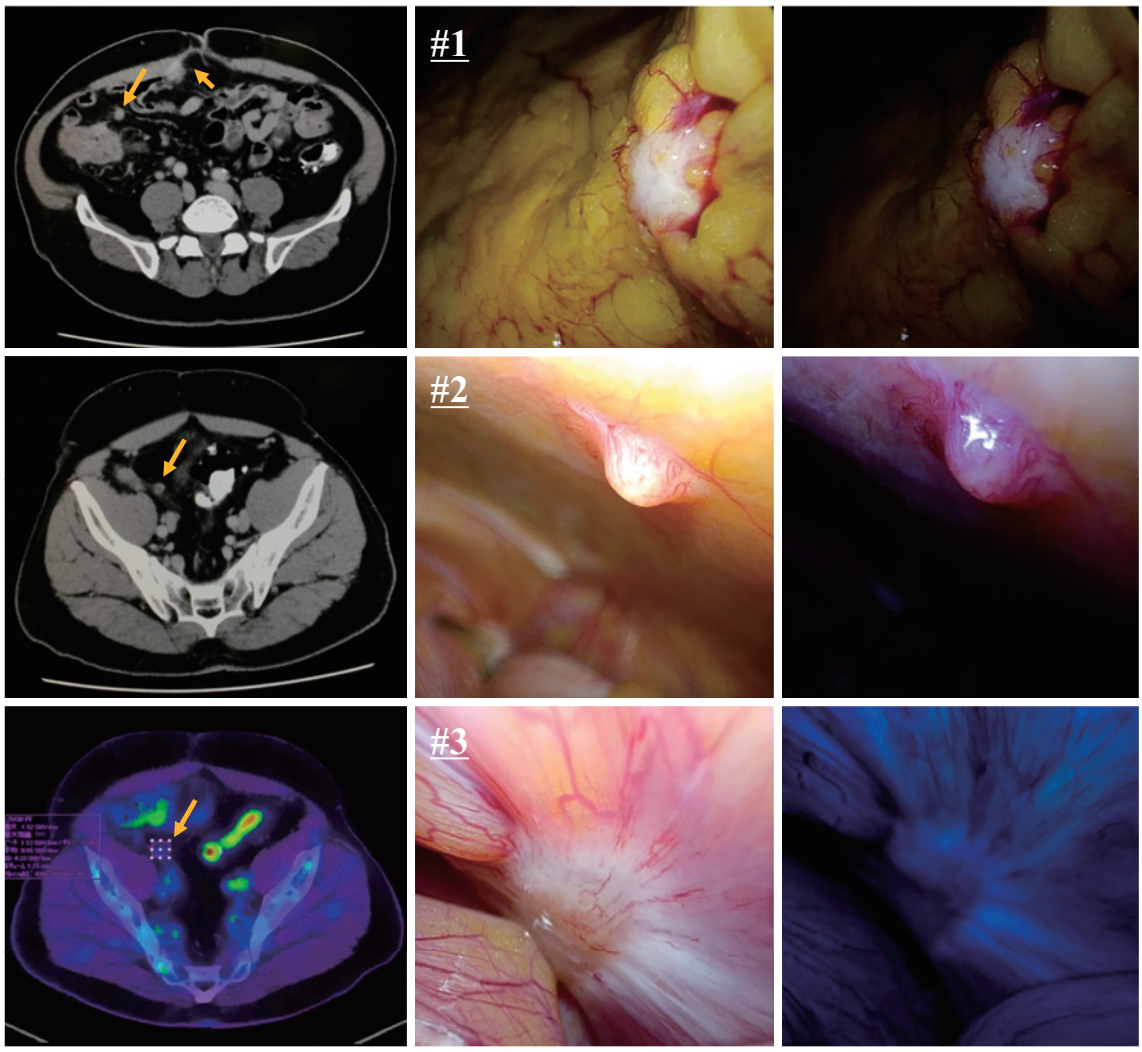

Figure 3. Case 5-the case of ascending colon cancer with peritoneal dissemination.
The dissemination was detected on CT and PET-CT before the surgery. It was difficult to find the appropriate distance from the tumor to the laparoscope and judge whether the nodule was positive or negative based on the fluorescence observation.

cross-sectional imaging method. MDCT has a detection rate of 54-67% for peritoneal dissemination, depending on the lesion size and localization.[14] MDCT, in combination with FDG-PET, has a sensitivity of 72%, specificity of 97%, and accuracy of 88%.[15] However, the detection ability reduces for micro-lesions and mucinous carcinoma and increases for non-malignant tumors, such as inflammatory diseases and foreign substances. Furthermore, the accuracy of the test reduces with poor blood glucose control. Therefore, the diagnostic ability is not robust.

Currently, if dissemination or metastasis is suspected during surgery, rapid intraoperative diagnosis using frozen specimens is performed when required. However, the small sample size and effects of freezing during sample preparation limit the level of diagnosis.[16, 17] The time taken (20-30 min) from sample preparation to diagnosis and the need for the presence of a pathologist further restricts diagnosis.

5-ALA has been covered by the national health insurance system in Japan since 2013 and is widely used in clinical practice for visualizing tumor tissues during tumor resection of malignant glioma in the field of neurosurgery. Since 2017 it has been widely used for non-muscle invasive bladder cancer (visualized by cystoscopy) in the field of urology. Currently, clinical research is ongoing in other fields, including, digestive and respiratory surgery, obstetrics, and gynecology. Adverse events with 5-ALA, such as hypotension and photosensitivity after the induction of anesthesia, have been re-

ported;[11] however, 5-ALA is an amino acid originally present in the body and generally considered safe.

In the field of digestive surgery, clinical research has demonstrated the effectiveness of laparoscopic diagnosis of peritoneal dissemination[6-8] and lymph node metastasis in gastric cancer,[18] peritoneal dissemination in pancreatic[19] and colorectal cancers,[10] and lymph node metastasis in colorectal cancer.[20] In the field of gastrointestinal endoscopy, diagnosis of gastric cancer[21, 22] and detection of dysplasia[23] have been attempted during lower gastrointestinal endoscopy in patients with ulcerative colitis.

To our knowledge, studies on peritoneal dissemination in colorectal cancer are scarce: two on intraoperative diagnosis by Kondo et al.[10] and Yonemura et al.[24] and one on laparoscopic diagnosis by Kondo et al.[10] Yonemura et al. performed PDD with 5-ALA during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in laparotomy patients with peritoneal disseminated cancer and several carcinomas. They reported a sensitivity of 53% and specificity of 100% in patients with colorectal cancer, and sensitivity of 17% and specificity of 100% in patients with appendix cancer.[24]

Performing PDD with 5-ALA has a few limitations: it is not quantitative, positive or negative judgments made are subjective, and observation conditions are unstable. In 2011, Kajimoto et al.[25] described the two major problems associated with PDD using 5-ALA: (1) quantification of fluorescence intensity based on parameters, including, fluorescence judgments, observation conditions, excitation light intensities, surgical fields, etc., and (2) resolving the mechanism of tumor-selective accumulation of PPIX. In 2019, Sakao et al.[26] reported fluorescence observation during thoracoscopic lung resection; they affirmed that a method for quantitative measurement of fluorescence was lacking and currently, only a subjective evaluation was done visually. They emphasized the need to establish quantitative measurement and objective evaluation methods for fluorescence levels and compared them with pathological findings. These issues, however, are still unresolved.

Intraoperative diagnosis with 5-ALA, in particular, is accompanied by the following issues: (1) quantification of fluorescence intensity (based on an objective index, histopathology-based quantification and comparison, and method established for reducing false positives and negatives), and (2) improvement of the observation environment (close-to-wide-angle observation, fluorescence enhancement, photobleaching, autofluorescence, interference (contrast), light intensity, fluorescence and white light balance [improvement of Scope/light source], optimum dose, and observation time setting).

In recent years, research on systems and equipment that enhances fluorescence,[27] quantitatively evaluates PPIX fluorescence intensity, eliminates autofluorescence,[18] and compares pathological tissues based on the degree of differentiation and histology[21] have been reported. The accuracy of inspection and the environment for observation is expected to improve in the future. In the field of neurosurgery, quantitative analysis of histological malignancy has been attempted using intraoperative rapid flow cytometry in combination with 5-ALA.[28]

The indications of PDD for colorectal cancer using 5-ALA should be explored further through clinical trials (initiated by a company or a doctor) to compensate for the paucity of data at present (12 cases reported by Kondo et al.[10] and 65 cases by Yonemura et al.[24]) However, data is insufficient for initiating a clinical trial. Therefore, we conducted an exploratory study (in the clinical study format) to clarify the application of PDD using 5-ALA for diagnosing peritoneal dissemination during laparoscopic surgery.

In this study, four of the six patients who underwent surgery had white nodules that were diagnosed as peritoneal dissemination lesions intraoperatively. However, only one case was pathologically proved to be cancer; therefore, the macroscopic diagnosis was not always correct. The case that was positive for PDD was consistent with pathological diagnosis.

A major limitation of this study is that the observation environment was changing and unstable.

The median time from oral administration of reagents to observation was 226 (97-296) min; the time varied because of difficulty in controlling the time of entry to the operating room. In the case of second and subsequent cases of surgery, it was difficult to adjust the oral administration time because the admission time was determined just before surgery. In case 5, the patient was admitted to the room immediately after taking the drug and was placed in the gastric tube immediately, so there was a possibility that a sufficient amount of the drug was not

actually absorbed. In addition, the observation conditions were not optimal; the image quality of the observation equipment was inferior to that of the 12 mm high-definition camera that was normally used because of incompatibility between the light source and scope (an old scope was used for observation).

Besides, during laparoscopic observation, it was difficult to observe the entire abdominal cavity in close proximity and judge whether the fluorescence emission was positive or negative due to the absence of an objective index. The photobleaching phenomenon may have occurred during continuous observation with fluorescent light, and hence, the light-emitting part could not be recognized.

Except for Case 5 diagnosed with peritoneal dissemination before surgery, no significant oversight of dissemination may have occurred considering that no obvious recurrence of peritoneal dissemination was observed during follow-up. However, a lesion might not have been detected because the peritoneal cavity was not completely observed.

In addition, the number of cases included were small, and the clinical research method enforced on April 1, 2018, made it difficult to procure reagents (5-ALA, in particular) from SBI Pharma Co., Ltd. Therefore, only six cases could be analyzed.

Currently, we believe that laparoscopic diagnosis of peritoneal dissemination of colorectal cancer with PDD using 5-ALA needs to be supported by other detection techniques. Determining whether a lesion is benign or malignant with white light and evaluating the exfoliated surface (tumor boundary), rather than detecting a new lesion would be helpful. Increasing the number of recruited patients might resolve various problems and aid in the development of an auxiliary diagnostic method. 5-ALA enhances radiosensitivity during colorectal cancer radiotherapy[29] and reduces the expression and infiltration of epidermal growth factor receptors (EGFR) in cancer cells.[30] We anticipate that in the future, these factors will be applied to photodynamic therapy (PDT).

Conclusion

We attempted PDD using 5-ALA during laparoscopic surgery for colorectal cancer.

To improve the accuracy, it is necessary to optimize the observation conditions, such as the accumulation of cases, observation method, and time from oral administration to observation.

Conflicts of Interest: SBI Pharma Co., Ltd. provided us with the reagent 5-aminolevulinic acid hydrochloride and light source (Aladuck®) free of charge.

Author Contribution: Fumi Maeda: Conceptualization, Methodology, Validation, Formal analysis, Writing-Original draft preparation, Visualization, Project administration.

Takeshi Ohki: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing-Reviewing and Editing

Yuji Inoue: Validation, Investigation.

Michio Itabashi: Supervision.

Masakazu Yamamoto: Supervision.

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