Surgical Treatment for Encapsulating Peritoneal Sclerosis: 24 Years’ Experience

Hideki Kawanishi
Department of Artificial Organs, Akane-Foundation, Tsuchiya General Hospital,

Abstract
Background: Encapsulating peritoneal sclerosis (EPS) is a serious complication of long-term peritoneal dialysis. The mortality rate for EPS is high, primarily due to complications related to bowel obstruction. Surgery was previously contraindicated; however, surgical enterolysis is performed for patients in whom bowel obstruction fail to improve.

Methods: This was a retrospective observational study of patients with EPS who received surgical intervention at a single center between November 1993 and October 2017. The severity of intestine damage was characterized by grade-3 peritoneal calcification on abdominal CT and degeneration of the small intestinal wall in surgery.

Results: Two-hundred and forty-three patients with EPS opted for surgery. Among them, 58 had recurrence and required re-surgery; a total of 318 EPS surgeries were performed. Death was related to EPS in 61 patients (25.1%), of whom 15 died postoperatively. Sixty-seven patients (27.6%) died from other causes. The actuarial survival rates at 1, 2, 3, 5, and 8 years after EPS diagnosis were 91%, 83%, 77%, 66%, and 53% respectively. The 50% actuarial survival points after EPS diagnosis and surgery were 104 months and 85 months, respectively. Peritoneal calcification and small intestinal wall degeneration grading showed significant association with the mortality curve for EPS-related death.

Conclusion: Excellent outcomes for EPS are achieved with surgery. The degree of peritoneal deterioration affected the clinical outcomes. Currently, EPS is no longer recognized as a fatal complication.

Key words: Peritoneal dialysis, EPS, Encapsulating peritoneal sclerosis, Surgery

Introduction
Encapsulating peritoneal sclerosis (EPS) and intraperitoneal inflammation leads to adhesive and inflammatory encapsulation of the intestinal tract, which then manifests as bowel obstruction syndrome. With the widespread use of PD, the number of patients developing EPS, a potentially fatal PD-related complication, has increased (1, 2). As a consequence, there is considerable debate whether an arbitrary expiry date for PD should be utilized due to the risk of EPS (3). However, recent clinical studies have clarified the pathogenesis of EPS and proposed therapeutic strategies (4,5).
Therapeutic options for EPS include corticosteroids, tamoxifen, and surgical treatment. The Dutch EPS guidelines suggest precise management options with respect to treatment with corticosteroids, tamoxifen, and surgery (6). However, medication therapy studies have included only a case series or small number of patients; thus, the clinical outcomes cannot be clearly concluded at present. Based on the National Institute for Health and Care Excellence Guidelines (NICE-GL), there is no clear evidence to support any particular medical therapy for treating EPS. Corticosteroids, immunosuppressants, and tamoxifen have been used, and may be implemented for treatment at the physician’s discretion (7).

Surgery was previously contraindicated in patients with EPS (8) and most patients treated surgically died due to technical complications. These deaths occurred by anastomosis failure because the pathogenesis of EPS was not well understood by surgeons, and, in many cases, simple resection of adherent intestinal loops with enterooanastomosis was performed (1,2); however, the final option for patients in whom bowel obstruction symptoms fail to improve is surgical enterolysis, which we have actively performed since 1993. In EPS, the intestine is degenerated and vulnerable, so the risk of intestinal perforation is high due to the persistent obstruction. Such occurrences are fatal. We therefore consider that surgery is indicated for all patients with EPS with severe symptoms of bowel obstruction (9-11).

In the present study, we investigated the experience of surgical therapy and long-term outcomes in patients with EPS who underwent surgical treatment at a single center between 1993 and 2017.

Methods
Study design and population

This was a retrospective observational study of patients with EPS who received surgical intervention at Tsuchiya General Hospital between November 1993 and October 2017. This study was approved by the Tsuchiya General Hospital Institutional Review Board for Human Investigation (approval number: E160530-1), and performed according to the principles of the Declaration of Helsinki. Written informed consent for surgical procedure and progress survey was obtained from each patient before surgery. EPS was defined by the ISPD ad hoc committee recommendation (4) and position paper for ISPD (12), and diagnostically confirmed by laparotomy or computed tomography (CT) imaging at base facilities before patients were referred to our center for surgical assessment. The indications for surgery were severe or repeat/progress bowel obstruction symptoms and malnutrition. Most cases had a planned admission; 4 were emergency cases due to intestinal perforation. Total parenteral nutrition (TPN) was performed in 183 patients (75.3%); 32 cases continued TPN until admission.

PD introduction time, PD withdrawal and catheter removal time, EPS onset time,
presence or absence of peritonitis, medication information (corticosteroid, immunosuppressant), and application of peritoneal lavage (13) was collected from the facility of initial admission. However, data on other medications, prescription of PD solution, peritoneal permeability, and effluent bio-marker were unable to be collected.

Preoperative examination and management

In a planned admission case, the following abdominal examination was performed in addition to the usual general anesthesia preoperative surgical examination. Enhanced CT of the abdomen was performed for assess the adhesion degree; a gastrointestinal fiberscope was used for examination of upper gastrointestinal lesions. A barium enema was undergone to confirm colon stenosis, and, if organotypic colon lesions were suspected, a colon fiberscope is used. Small intestine fluoroscopy was performed if severe obstruction was not observed, to confirm the presence of stricture.

A fully preoperative dietetic assessment was completed, and patients received TPN one week before surgery. Three or four days before surgery, a Miller-Abbott ileus tube was inserted, and intestinal decompression was performed. This Ileus tube is indispensable for confirming the integrity of the small intestine for passage after enterolysis, and to assess any damage to the intestine. Therefore, a tube without a protrusion at the tip of the Ileus tube was selected.

Surgical technique

Laparotomy with a midline abdominal incision was accomplished. Considering the mechanism of EPS development, this surgical technique is simple, involving only the division of peritoneal adhesions by repeated decorticat ion of fibrous membranes with a sharp instrument, usually scissors and a scalpel. To identify the site of stenosis, we have begun inserted, after enterolysis, a Miller-Abbott ileus tube with an inflated balloon from the jejunum to ileum.

Surgery can reverse the bowel obstruction, but it does not improve the peritoneal deterioration. As a result, the capsules can re-form, with EPS recurrence in some patients 6–24 months later (11). In addition, adhesions also occur as a result of surgical injury to the intestinal wall and mesenteric serosa. To prevent recurrence, we have been performing the Noble plication procedure since April 2007 (14, 15), in which the intestine is sutured to prevent re-obstruction of the bowel. This technique prevents not only passage disturbances resulting from kinking and adhesion of the small intestine, but also adhesions in and escape into the pelvic cavity.

Patients experiencing recurrence or insufficient adhesiolysis from intestinal wall calcification and/or serious deterioration require side-to-side bypass anastomosis between the oral site jejunum and transverse colon. The area for anastomosis is selected as the part of the small intestinal wall with the least deterioration, and obstruction improved by adhesion peeling. For that
reason, most anastomosed areas were performed at a point 30 to 100 cm distal to the Treitz ligament. Prior to or after surgery, enterostomy was additionally performed in cases where intestinal perforation was observed. After surgery, patients are managed by incorporating TPN; ileus tube withdrawal around 1 week and oral intake initiation is undergone in stable patients.

Assessment of severity of intestinal damage by preoperative CT and intraoperative findings

The severity of intestinal damage was assessed retrospectively at the time of initial surgery. Peritoneal calcification was classified into three stages (1 to 3) according to preoperative CT and intraoperative findings. Regarding calcification amount, grade 1, 2, and 3 were <50%, 50-80%, and ≥80% calcified, respectively. The preoperative CT evaluation was performed by one radiologist, one nephrologist, one surgeon, and the intraoperative findings were evaluated by the surgeon. The grade of calcification is show in supplemental Fig. 1.

The degeneration/deterioration grade of small intestinal wall was evaluated macroscopically based on the dryness, wrinkling, color (if light brown), and hardness, and classified into 3 levels according to intraoperative findings as follows: Grade 1, mild abnormal and soft; Grade 2, whole circumference/partial degeneration in several parts, especially in the ileum; Grade 3, highly degenerated in almost all areas (supplemental Fig. 2). Evaluation was accomplished by a main surgeon and two assistant surgeons and obtained from the surgical record.

Outcomes after surgery

In October 2017, a survey was mailed to all patients who underwent as part of the outcomes investigation. For cases without replies, a survey was sent to the facility of initial admission. The survey content included outcomes and the course of abdominal symptoms after surgery. EPS-related death was defined as death by malnutrition and inflammation of bowel obstruction, and peritonitis.

Statistics

Data were analyzed using SPSS version 25 (IBM corporation, Armonk, NY USA). Continuous variables are described as median and range, and categorical variables are described as absolute numbers and proportion. Survival from EPS onset to follow-up were calculated using the Kaplan-Meier method. The severity of EPS and survival curve of EPS-related death were compared using the log rank test. A difference was considered significant when the p value was less than 0.05.

Results

Surgical cases
Between November 1993 and October 2017, 243 patients with EPS were admitted for surgery into 165 facilities, including three overseas facilities, before transfer to our center. Among them, 58 patients (23.9%) had recurrence and required re-surgery; a total of 318 EPS surgeries were performed (Fig. 1). The number of annual surgical cases increased yearly until 2007, but then began decreasing.

Among 146 male (60.0%), 4 had diabetes at EPS diagnosis. The age at PD initiation was 41 years, and the PD duration was 127.7 months, including 8 cases of kidney transplantation. Sixteen cases (6.6%) used neutral low glucose degradation products (GDPs) solution at the start of PD. The incidence of peritonitis during PD was median of 2 times, and 60 patients showed no peritonitis. The period from PD withdrawal to EPS onset was 26.6 months, and 229 cases (94.2%) had EPS after PD withdrawal. From EPS onset to surgery the was 15.3 months. Fifty-eight patients (23.9%) underwent peritoneal lavage after withdrawal of PD; the median lavage period was 14.3 months. In 175 patients (72.0%) using corticosteroids, the treatment ranged from methylprednisolone pulse therapy to oral prednisolone 10-60 mg/day depending on the patient (Table 1). No patient used tamoxifen.

Surgical results

Of the 15 patients (6.2%) who died postoperatively, sepsis resulting from intestinal perforation/dysraphia (8 patients), infection (3 patients), malnutrition (3 patients) and hepatic failure (1 patient) were the causes of death. Enterolysis was performed in 240 surgeries. Bypass anastomosis between the jejunum and large intestine was performed in 40 patients in whom complete enterolysis could not be performed or because of the risk of recurrence. In 4 patients with localized adhesions and mild degeneration of the small intestine wall, the adhered small intestine was resected and anastomosed (enterectomy and enteroenterostomy). Two patients with intestinal perforation before and after surgery underwent enterostomy. Three did not undergo enterolysis, because, although there was a high degree of intestinal peritoneal deterioration, no capsule was observed.

Surgery for recurrence was performed in 58 patients (23.9%). These re-surgeries were conducted at 20 months (range: 2-99 months) after the first surgery. Re-surgery was performed once in 46 patients, twice in 9 patients, 3 times in 2 patients, and 5 times in 1 patient, for a total of 75 re-surgeries. Enterolysis was performed in 75 recurrent surgeries. Bypass between the jejunum and large intestine (22 patients) or ileum (1 patient) was performed in 23 patients. Two patients who had intestinal perforation before and during surgery underwent enterostomy (Table 2).

Long-term outcomes
By the end of the study period, 128 patients (52.7%) had died, among which 61 were EPS-related deaths (25.1%), and 15 were deaths related to surgery (6.2%). Other causes of death were observed in 67 patients (27.6%) (Supplemental Table 1). However, some EPS-related symptoms remained in 11 patients (9.9%) of the 111 survivors, excluding 4 lost to follow-up.

The median observation periods after EPS diagnosis and EPS surgery were 76 (0-353), and 69 (49-290) months, respectively. The actuarial survival rates at 1, 2, 3, 5, and 8 years after EPS diagnosis were 91%, 83%, 77%, 66%, and 53%, respectively (Fig 2). The 50% actuarial survival points after EPS diagnosis and surgery were 104 and 85 months, respectively. The mortality rates for EPS-related death at 1, 2, 3, 5, and 8 years after EPS diagnosis were 5%, 10%, 13%, 20%, and 28%, respectively (Fig 2).

Peritoneal calcification grade showed a significant association with the mortality curve for EPS-related death (Fig 3a) (grade 1 and 2, p<0.0015; grade 1 and 3, p<0.0065). Additionally, the degree of small intestinal wall degeneration exhibited a significant association with the mortality curve for EPS-related death (Fig 3b) (grade 1 and 2, p<0.0452; grade 1 and 3; p<0.0008, grade 2 and 3, p<0.0058).

Discussion

In this single center long-term study, we found that active EPS surgery improved patient outcomes. Experience of over 20 years at a single center and by the same surgeon seems to be involved in the improvement of surgical techniques and procedures. However, the most significant factor for improved outcomes is the extent of peritoneal deterioration. Especially, the degree of peritoneal calcification and intestinal wall degeneration increased surgical difficulty and had the greatest influence on outcomes. The basis that EPS severity is a factor determining outcomes was shown in Figure 3.

The usefulness of abdominal CT in EPS diagnosis has been reported (16, 17). Scoring is performed based on calcification, thickening, tethering, location, and bowel dilatation, which is useful for diagnosis of established symptomatic-EPS; however, confirming diagnosis in patients with asymptomatic EPS is difficult. In particular, bowel tethering and peritoneal calcification were shown to be effective for EPS diagnosis. Additionally, in our study, peritoneal calcification on abdominal CT before initial surgery was evaluated by the modified scoring system by Tarizi (16). Tarizi's scoring seems to be evaluating including the parietal peritoneal calcification, but findings affecting the clinical symptoms (bowel obstruction) including calcification of the visceral peritoneum and dissociation from clinical symptoms should be considered (17). Therefore, we classified it EPS into 3 grades for a more appropriate scale than the Tarizi classification. The extent of peritoneal calcification as well as extent of bowel wall degeneration affected postoperative outcomes. Furthermore, the score obtained by totaling
peritoneal calcification and intestinal degeneration was also correlated with outcomes (data not shown).

One issue of EPS surgery is postoperative recurrence, and our results also indicated that 23.9% of patients required re-surgery at a median 20 months postoperatively. Therefore, in order to prevent kinking of the intestinal tract after adhesion peeling, we have carried out the classical ileectomy surgical procedure of Noble plication since 2007, which rendered a slight decrease in the recurrence rate; thus, it has been applied to all patients thereafter (11).

Peritoneal calcification and intestinal degeneration determine the difficulty of surgery and prognosis (including recurrence) and were also an aspect of the surgical experience. From around 2007, patients with incomplete adhesion exfoliation, bypass anastomosis between delaminating small intestine, and transverse colon were actively added. Deciding whether to add an anastomosis in the presence of advanced intestinal deterioration is concerning. Diarrhea caused by short bowel syndrome is frequent as it anastomoses in the upper small intestine. Many patients improve in a few months, but some patients see persistence. We also experienced patients where the symptoms of intestinal obstruction were not ameliorated by narrowing of the anastomotic site and kinking of the small intestine of the oral side. In that case, percutaneous endoscopic gastrostomy and/or jejunal extension was carried out and managed with TPN at home (18). Based on our experiences, we recognize that enterolysis in EPS differs depending on individual patient characteristics, including various factors such as grade of peritoneal deterioration, calcification, and adhesion range. Therefore, selection of a suitable surgical technique based on the individual adhesion grade and skill of the surgeons are essential.

Neutral low GDPs solution has been shown to prevent peritoneal deterioration (19-21) and reduce the risk of EPS development (22). Many factors such as hypertonic glucose, osmotic pressure, and lactate are considered as causes of peritoneal deterioration as well as GDPs (4, 5). In this study, the number of patients using neutral solution from the introduction phase was as few as 16 and no difference in outcomes to acidic solution could be recognized. Although a long-term PD period of 8 years or more is indicated in acidic solution use as increasing the risk of EPS (2), neutral solution has been used for all patients for more than 10 years in Japan, and patients on long-term neutral solution are maintained. In this study, the number of patients who undergo surgery for EPS has been declining since 2008. Although the risk factors for EPS are multifactorial, the use of neutral solution may be involved in the reduction of EPS risk in surgical cases.

The postoperative outcomes of this survey were almost the same as the previous report on 181 patients in 2011 (11), and the overall and EPS-related mortality rate at 5 years (34% and 20%, respectively) were better than that of other reports mainly based on conservative therapies (23, 24, 25). The aggressive surgical treatment for EPS was started in UK (26), German (27, 28),
and Dutch (29) facilities. Their EPS overall mortality rate is consistent with that of our results at 32–35%. Currently, surgical treatment has been carried out for EPS in many facilities in Japan, and the Japanese Renal Data Registry shows that 81% of the EPS cases involved some form of surgical treatment (30).

In consideration of these surgical results and based on an ISPD-position paper (12) and NICE-GL (7), the patients with suspected EPS should be referred or discussed early with units who have expertise in EPS surgery. Surgery should be performed by teams experienced in EPS surgery.

There are several limitations in this study. First, it is a single-center retrospective study without non-surgical EPS patients assigned as a control group. However, it is based on more than 20 years’ experience by the same surgical team who is well versed in dialysis therapy and EPS, and improvement of surgical technique due to case experience are advantage to surgical outcomes. Second, because the majority of patients are managed in other facilities, information on PD management, effluent bio-markers, peritoneal permeability and other variables are uncertain; thus, no conclusion on EPS predictive factors has been made. Third, the severity of peritoneal deterioration—peritoneal calcification and intestinal degeneration—indicates that it affects the surgical results but is a finding at the initial surgery; thus, the influence of recurrent surgery is not taken into consideration. Additionally, the extent of deterioration of the intestinal wall is determined by the subjective judgment of the surgeon. Furthermore, surgical techniques have advanced with each successive case, and their techniques effects are not taken into consideration. However, the degree of adhesion and capsule of EPS varies depending on the patient, and we believe that the highest quality surgery possible was done for each patient. Regardless of these limitations, the greatest strengths of this study are the introduction of a surgical therapy for EPS that was previously unsupported by clinicians and the presentation of this therapy’s long-term outcomes.

In conclusion, EPS surgical experience and outcomes during 24 years in a single center were reported; patients who undergo the surgery showed better outcomes. The increase in surgical treatment rate in the world promoted improvements in countermeasures against and better understanding of EPS. Currently, EPS is no longer recognized as a fatal complication.

Acknowledgments

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Figure 1. Surgical case from 1993 to 2017

- Black bar; first surgery case, gray bar; re-surgery case
The actuarial survival rate at 1, 2, 3, 5, and 8 years after EPS diagnosis was 91%, 83%, 77%, 66%, and 53%, respectively. The mortality rate for EPS-related death at 1, 2, 3, 5, and 8 years after EPS diagnosis was 5%, 10%, 13%, 20%, and 28%, respectively.

Mortality curve for EPS-related death, a) evaluation of peritoneal calcification grade (log rank test, grade 1 and 2, \( p < 0.0015 \), grade 1 and 3, \( p < 0.0065 \)), b) evaluation of degeneration grade of small intestinal wall, (log rank test, grade 1 and 2, \( p < 0.0452 \), grade 1 and 3, \( p < 0.0008 \), grade 2 and 3 \( p < 0.0058 \)).
Table 1. EPS treated with Surgery, 1993 – 2017

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Total patients (n)</td>
<td>243</td>
</tr>
<tr>
<td>Total surgeries (n)</td>
<td>318</td>
</tr>
<tr>
<td>Patients undergoing multiple surgeries [n (%), times]</td>
<td>58 (23.9), 75</td>
</tr>
<tr>
<td>Facility of initial admission (n)</td>
<td>165 (outside Japan 3)</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>146 (60.0)</td>
</tr>
<tr>
<td>Diabetes [n]</td>
<td>4</td>
</tr>
<tr>
<td>Facility of initial admission (n)</td>
<td>165 (outside Japan 3)</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>146 (60.0)</td>
</tr>
<tr>
<td>Diabetes [n]</td>
<td>4</td>
</tr>
<tr>
<td>Age at PD start [years (range)]</td>
<td>41.0 (0-68)</td>
</tr>
<tr>
<td>PD duration [months (range)]</td>
<td>127.8 (22.1-274.6)</td>
</tr>
<tr>
<td>Patients of completely use neutral PDS [n (%)]</td>
<td>16 (6.6)</td>
</tr>
<tr>
<td>Peritonitis rate (times (range))</td>
<td>2.0 (1-10) a</td>
</tr>
<tr>
<td>PD withdrawal to EPS onset [months (range)]</td>
<td>26.6 (0.5-248.5) b</td>
</tr>
<tr>
<td>Cases of EPS onset after PD withdrawal [n (%)]</td>
<td>229 (94.2)</td>
</tr>
<tr>
<td>PD catheter replace to EPS onset [months (range)]</td>
<td>36.0 (0-234.4) b</td>
</tr>
<tr>
<td>EPS onset to surgery [months (range)]</td>
<td>15.3 (1-234.4)</td>
</tr>
<tr>
<td>Patients given post-PD peritoneal lavage [n, (%)]</td>
<td>58 (23.9)</td>
</tr>
<tr>
<td>Lavage duration [months (range)]</td>
<td>14.3 (2-52.8)</td>
</tr>
<tr>
<td>Patients given corticosteroids after EPS onset [n (%)]</td>
<td>175 (72.0)</td>
</tr>
</tbody>
</table>

PD: peritoneal dialysis.
PDS: peritoneal dialysis solution

a) Excludes cases of non-peritonitis.
b) Excludes cases experiencing EPS onset during peritoneal dialysis.

Variable data indicate median and range.
Table 2. Surgical procedures for EPS
First surgery 243 patients
   Enterolysis : 240
      + Bypass anastomosis between the jejunum and large intestine : 40
      + Enterectomy and enteroenterostomy: 4
      + Enterostomy: 2
   No enterolysis: 3

Recurrent 75 times on 58 patients
   Enterolysis: 75
      + Bypass anastomosis between the jejunum and large intestine: 22
      + Enteroenterostomy: 1
      + Enterostomy: 2

Supplemental Table 1, Cause of death in surgical EPS patients in 1993-2017

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>243</td>
<td></td>
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<tr>
<td>Total death</td>
<td>128</td>
<td>(52.7%)</td>
</tr>
<tr>
<td>EPS related death</td>
<td>61</td>
<td>(25.1%)</td>
</tr>
<tr>
<td>Post-surgical death</td>
<td>15</td>
<td>(6.2%)</td>
</tr>
<tr>
<td>Long-term death</td>
<td>46</td>
<td>(93.8%)</td>
</tr>
<tr>
<td>Other cause death</td>
<td>67</td>
<td>(27.6%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>30</td>
<td>(44.8%)</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>5</td>
<td>(7.5%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>(10.4%)</td>
</tr>
<tr>
<td>Intestinal disease</td>
<td>5</td>
<td>(7.5%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
<td>(13.4%)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>4</td>
<td>(6.0%)</td>
</tr>
<tr>
<td>Suicide</td>
<td>3</td>
<td>(4.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>(6.0%)</td>
</tr>
<tr>
<td>Loss to follow up</td>
<td>4</td>
<td>(1.6%)</td>
</tr>
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</table>
Supplement Figure 1. The photo of peritoneal calcification grade on CT

Grade 1  Grade 2  Grade 3

The calcification area on abdominal CT, were <50%, 50-80%, and ≥80% calcified, respectively. Intraoperative findings of intestinal calcification grade 3 is showed.
Supplement Figure 2. The photo of degeneration/deterioration grade of small intestinal wall

Grade 1: mild abnormal and soft; Grade 2: whole circumference/partial degeneration in several part, especially in the ileum; Grade 3: highly degenerated in almost all aria, Upper figure; before enterolysis, lower figure; after enterolysis