Author's response to reviews

Title: Successful treatment of recurrent small bowel adenocarcinoma by cytoreductive surgery and chemotherapy: a case report and review of the literature

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Author's response to reviews: see over
Dear Dr. Kidd:

Please find enclosed our manuscript titled Successful treatment of recurrent small bowel adenocarcinoma by cytoreductive surgery and chemotherapy: a case report and review of the literature as a Case report for publication in Journal of Medical Case Reports. We have revised the manuscript according to the reviewers’ comments. Changes to the revised manuscript have been described point by point.

Referee 1:

Concern: It is not clear what the authors mean in the third sentence when they describe lack of movement of the ileus tube.

Response: Lack of movement of the ileus tube means stoppage of movement of ileus tube. We have made this change in the revised manuscript.

Concern: What type of discussion took place with the patient regarding the extent of surgery and the likelihood of its success in delivering prolonged survival or cure?

Response: We have added the following sentences to answer the concern.

Levine et al showed that the primary tumor site, performance status, resection status, and development of complications predicted outcomes [19]. Although the extent of our cytoreductive surgery was less than that of the complete cytoreductive surgery by Marchettini et al and Jacks et al., we resected all visible tumors. This patient survived for an extended period with good performance status (0), good resection status, and no complications.

Concern: The discussion could be improved by reference to recently published articles (a) Overman M J. Recent Advances in the Management of Adenocarcinoma of the small intestine Gastrointest Cancer Res 2009; 3: 90-96;(b) Dasari BVM, Gardiner KR. Management of Adenocarcinoma of the small
Response: We have improved the discussion according to the referee’s advice. We have introduced complete cytoreductive surgery with intra-operative intraperitoneal chemotherapy as an effective treatment for SBA peritoneal carcinomatosis and compared our procedure to the original procedure. We have added the recommended articles to the Reference section.

Referee 2:

Concern: The authors present a case of small bowel adenocarcinoma treated with good short term follow up with cytoreductive surgery and systemic chemotherapy. The case is not novel (as suggested in the introduction). There have been 2 series reported of cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for peritoneal dissemination from small bowel carcinoma (from Washington Center Hospital and Wake Forest University). These should be addressed in the discussion.

Response: We have addressed the description regarding cytoreductive surgery with intraperitoneal hyperthermic chemotherapy as an effective treatment for peritoneal dissemination from SBA. We have added the citations to the Reference section.

Concern: Quality of written English: Needs some language corrections before being published.

Response: The paper has been proofread by two native English editors who specialize in editing manuscript written by Asian scientists.
The following changes (red ink and underlined) have been made to the manuscript.

**Title:** Successful treatment of recurrent small bowel adenocarcinoma by cytoreductive surgery and chemotherapy: a case report and review of the literature

**Abstract**

**Introduction**

Small bowel adenocarcinoma is a rare malignancy associated with a poor prognosis, and there is weak evidence of effective treatment.

**Case presentation**

We report on a 72-year-old female who developed a peritoneal metastasis from recurrent small bowel adenocarcinoma after curative resection and adjuvant chemotherapy with S-1 and polysaccharide K.

Subsequently, no sign of recurrence was observed for 42 months after the second operation.

**Conclusion:** This is the first case report of the successful treatment of peritoneal metastasis from small bowel adenocarcinoma by cytoreductive surgery and combination chemotherapy (folinic acid/fluorouracil/oxaliplatin and folinic acid/fluorouracil/irinotecan with polysaccharide K).

**Introduction**

Adenocarcinoma is the most common malignancy of the small bowel, comprising about one-third of all small bowel malignancies [2].

The most frequent location for small bowel adenocarcinoma (SBA) is the duodenum (52−55%), followed by the jejunum (18−25%), ileum (13%), and not otherwise specified (10−14%) [2,3].

Non-specific symptoms and the lack of useful diagnostic methods results in a delayed diagnosis of SBA.

The ratio of SBA diagnosed at stage I, stage II, stage III, and stage IV has been reported to be
4–12%, 20–27%, 26–39%, and 32–35%, respectively [2,3].

The 5-year survival rate is 26–30%, with a median survival of 20 months [2,3]. Although curative resection is the most important prognostic factor, 67% of patients with SBA receive curative resection [2,3].

Even after curative resection, 39% of patients develop recurrence [3].

The usefulness of adjuvant chemotherapy after curative resection or palliative chemotherapy for advanced or recurrent SBA remains unconfirmed because of the absence of a randomized control trial (RCT) regarding SBA [4,5]. (We have modified the citations.)

Only a few controlled clinical studies for SBA treatment have been reported [6,7], but the effectiveness of chemotherapy for advanced SBA has been shown by retrospective studies [8]. (We have modified the citations.)

Aggressive surgical intervention seems to be effective for some cases of advanced or recurrent SBA [9,10]. (We have modified the citations.)

We report on a patient who had peritoneal metastasis from recurrent SBA after curative surgery and adjuvant chemotherapy.

**Case Presentation**

A 70-year-old Japanese female was referred to our hospital to evaluate a small bowel obstruction. (The ethnicity of the patient was described.)

An upper gastrointestinal barium study and stoppage of ileus tube movement demonstrated a tumor in the jejunum near the ligament of Treitz. During surgery, we found the jejunal tumor located 20 cm away from the ligament of Treitz.

We performed an enterectomy, including the regional mesentery and a hysterectomy.

The jejunal tumor was a moderately differentiated adenocarcinoma, penetrating the small bowel wall.
The tumor was diagnosed as stage II according to the American Joint Committee on Cancer staging system.

Although the usefulness of adjuvant chemotherapy for SBA has not been confirmed due to the lack of RCTs, recurrence after curative resection of SBA is very high [3,4,8]. (We have modified the citations.)

S-1 has been confirmed as an effective reagent for gastric cancer after curative surgical resection [11]. (We have modified the citations.)

PSK has been confirmed as an effective adjuvant for gastric cancer as well as colorectal cancer (CRC) after curative resection [12,13]. (We have modified the citations.)

Although body computed tomography (CT) and contrast magnetic resonance imaging (MRI) displayed no sign of recurrence, the CEA level was elevated to 8.9 ng/mL the following month.

A careful evaluation of her medical history disclosed hematuria at that time.

Histology of the bladder tumor resected transurethrally revealed a moderately differentiated adenocarcinoma invading from outside the bladder.

A colonoscopy showed tumors in the sigmoid colon and rectum, but not in the ascending colon.

A histological analysis revealed that these tumors were well-differentiated adenocarcinomas, indicating peritoneal dissemination of SBA.

We performed a laparotomy to confirm peritoneal dissemination and reduce the number of disseminated tumors because cytoreductive surgery has been shown to be useful in some cases of peritoneal carcinomatosis from SBA [9,10]. (We have modified the citations.)

During surgery, we found two sigmoid colon tumors, one rectal tumor and one bladder tumor, identical to the preoperative diagnosis (Fig. 1).

The nodule in the larger omentum was confirmed to be an adenocarcinoma by intraoperative rapid pathological diagnosis.

We resected these tumors, including a total cystectomy, rectosigmoidectomy, and omentectomy.
An immunohistochemical examination of cytokeratin (CK) 7 and CK20 exhibited CK7 (+)/CK20 (-) tumors in the primary and metastatic lesions.

This result differed from the profile of CK7/CK20 in CRC and was compatible with the profile of CK7/CK20 in SBA reported previously [14]. (We have modified the citations.)

The effectiveness of palliative chemotherapy for advanced SBA has been shown by retrospective studies [8,15-17]. (We have modified the citations.)

After the second operation, the patient received 12 cycles of FOLFOX with PSK until the peripheral neuropathy became severe.

After this regimen, five cycles of FOLFIRI with PSK were continued until no sign of recurrence was confirmed by PET, CT, and laboratory data 12 months after the second operation.

The patient survived with no sign of recurrence for 42 months after the second operation.

Discussion

This rarity is associated with a poor prognosis, lack of standard treatment, and an absence of RCTs [5,18]. (We have modified the citations.)

In the largest retrospective study, chemotherapy with 5-FU and a platinum compound was more effective than other chemotherapy combinations [15]. (We have modified the citations.)

A recent prospective study showed the usefulness of capecitabine and oxaliplatin for advanced SBA [7]. (We have modified the citations.)

SBA treatment is usually extrapolated from CRC or gastric cancer treatment.

Although the first treatment involving S-1 and PSK was ineffective, the second treatment using cytoreductive surgery and chemotherapy with FOLFOX/FOLFIRI plus PSK was very effective.

Irinotecan has been used for advanced SBA and has shown effectiveness in those cases [8,16,17]. (We have modified the citations.)

Cytoreductive surgery including parietal peritonectomy with intraperitoneal hyperthermic chemotherapy has demonstrated the effectiveness of peritoneal dissemination for abdominal
malignancies including advanced SBA [9,10,18]. Levine et al showed that the primary tumor site, performance status, resection status, and development of complications predicted outcomes [19]. Although the extent of our cytoreductive surgery was less than that of the complete cytoreductive surgery by Marchettini et al and Jacks et al., we resected all visible tumors. This patient survived for an extended period with good performance status (0), good resection status, and no complications. The pattern of peritoneal carcinomatosis from SBA resembles that from CRC more than from gastric cancer. (We have improved the discussion according to the referee’s advice.)

An extrapolation of CRC treatment to SBA treatment seems necessary before confirming a standard treatment.

Figure legends

Fig. 1: Resected colon specimen. Resected colon specimen revealed three tumors in the sigmoid colon and one tumor in the rectum. The features indicated that these were submucosal tumors.

Fig. 2:

Hematoxylin-eosin staining showed a moderately differentiated adenocarcinoma in the rectal tumor. The mucosa was not affected by the tumor, thus indicating that this tumor did not originate from the rectal mucosa.

The rectal tumor was strongly positive for cytokeratin (CK) 7, whereas the normal mucosa was negative for CK7.

The rectal tumor was negative for CK20, whereas the normal mucosa was positive for CK20.

We hope these changes will make the manuscript acceptable for publication. We look forward to hearing your response.

Sincerely,