**Prospective small bowel mucosal assessment immediately after chemoradiotherapy of unresectable locally advanced pancreatic cancer using capsule endoscopy: Case series**

Takeshi Yamashina1,5, Ryoji Takada2, Noriya Uedo1, Tomofumi Akasaka1, Noboru Hanaoka1, Yoji Takeuchi1, Koji Higashino1, Tatsuya Ioka3, Ryu Ishihara1, Teruki Teshima4, Kinji Nishiyama4 and Hiroyasu Iishi1

Departments of 1Gastrointestinal Oncology, 2Pancreatic Oncology, 3Cancer Survey and 4Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan

5Gastroenterology and Hepatology, Osaka Red Cross Hospital, Osaka, Japan

Corresponding author

Hiroyasu Iishi, MD

Department of Gastrointestinal Oncology

Osaka Medical Center for Cancer and Cardiovascular Disease

1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan

Tel.: +81-6-6972-1181, Fax: +81-6-6981-4067

Email: [iisi-hi@mc.pref.osaka.jp](mailto:iisi-hi@mc.pref.osaka.jp)

Guarantor of the article: Hiroyasu Iishi, MD

Financial support: T. Yamashina received five capsule endoscopies from Company Covidien (Dublin, Ireland). The other authors declare that they have no conflicts of interest.

Potential competing interests: None.

Author contributions

Conception and design: Takeshi Yamashina, Hiroyasu Iishi

Analysis and interpretation of the data: Takeshi Yamashina, Ryoji Takada, Noriya Uedo

Drafting of the article: Takeshi Yamashina, Teruki Teshima

Critical revision of the article for important intellectual content: Takeshi Yamashina

Final approval of the article: Takeshi Yamashina, Ryoji Takada, Noriya Uedo, Tomofumi Akasaka, Noboru Hanaoka, Yoji Takeuchi, Koji Higashino, Tatsuya Ioka, Ryu Ishihara, Teruki Teshima, Kinji Nishiyama and Hiroyasu Iishi.

Abstract

In this case series, three consecutive patients with unresectable locally advanced pancreatic cancer (ULAPC) underwent capsule endoscopy (CE) before and after chemoradiotherapy (CRT) to evaluate duodenal and jejunal mucosa, and examine the relationship between CE findings and dose distribution. CE after chemoradiotherapy showed duodenitis and proximal jejunitis in all three patients. The most inflamed region was the third part of the duodenum, and in dose distribution, this was the closest region to the center of irradiation. This case series shows that CE can safely diagnose acute duodenitis and proximal jejunitis caused by CRT for ULAPC, and the dose distribution is possible to predict the degree of duodenal and jejunal mucosal injuries.

*Key word*: radiation enteritis, capsule endoscopy, pancreatic cancer.

Introduction

In patients with unresectable locally advanced pancreatic cancer (ULAPC), chemoradiotherapy (CRT) is one of the effective standard therapies for ULAPC[1]. Despite the increasing numbers of cases of pancreatic cancer and patients undergoing radiotherapy (RT), there are only a small number of reports on the adverse gastrointestinal effects, especially radiation enteritis (RE).

**Case Report**

From August to November 2014, three patients (Patient A is a male in his 60’s, patient B is a female in her 70’s and patient C is a male in his 60’s) with ULAPC in the head of the pancreas were treated at the our hospital. All three patients provided written informed consent on all procedures associated with the study. The patient characteristics and lesions are shown in Table 1. Patient A received 1000 mg/m2 gemcitabine, and Patients B and C received 1000 mg/m2 gemcitabine plus 100mg/m2 nab-paclitaxel intravenously beginning on the first day of RT, then weekly thereafter during radiation. The radiation dose was 1.8 Gy/day, 5 days per week, with a total dose of 50.4 Gy administered in 28 fractions over 5.5 weeks using 10 MV X-rays. Three-dimensional conformal RT was used at five different portals. Gross tumor volume (GTV) was contoured at both expiration and inspiration phases on computed tomography simulation. Clinical target volume (CTV) included GTV with 5-mm margins and planning target volume (PTV) included CTV with 5-mm margins (Figure 1). During treatment, all three patients try to avoid using non-steroidal anti-inflammatory drugs to prevent NSAIDs-caused ulcers. Evaluation of the entire small intestine was carried out immediately before and immediately after CRT,. CE showed duodenitis and proximal jejunitis, and did not show enteritis in other area. Congested, erythematous and partially depleted mucosa was found in all three patients, and a small area of bleeding was seen in Patients B and C (Figures 2, 3 and 4). In all three patients, the most inflamed region was the third part of duodenum, and in terms of dose distribution, this was closest to the center of irradiation (Figures 1, 2, 3 and 4). These findings were not seen by CE before CRT. There was no significant stenosis and capsule retention did not occur. The Lewis score after CRT in Patients A, B and C was, 641, 4396 and 782respectively , and the scores were higher than before CRT in all three cases. The percentage volume of the duodenum receiving ≥45 Gy (V45) in Patients A, B and C was 23, 30 and 36%, respectively (Table 3). During treatment, we observed anorexia (grades 1 or 2 according to CTCAE) in all three patients.

**Discussion**

This is believed to be the first reported prospective case series of acute RE investigated by CE before and after CRT for ULAPC. Acute RE has been reported in 20–75% of patients as a complication of RT for abdominal or pelvic malignancies[2,3]. However, it was mainly acute radiation ileitis and there are few reports of duodenitis and jejunitis caused by CRT for ULAPC. In the present study, the patients were checked for any duodenal or small intestinal abnormality by CE before undergoing CRT, to enable evaluation of any injury caused by RT. CE showed that injury extended more deeply in the proximal jejunum than the duodenum in all three cases. These jejunal injuries cannot be seen by esophagogastroduodenoscopy, and CE is useful and safe for acute-phase evaluation of patients with CRT for ULAPC.

The third part of the duodenum was more inflamed than the other parts of duodenum and proximal jejunum, and this might be significantly related to the dose distribution of radiation. In relation to the dose distribution and percent V45, the third part of the duodenum was exposed to the highest level of radiation in the duodenum and proximal jejunum, and it was the closest region to the pancreatic head. The dose distribution might be possible to predict the degree of duodenal and jejunal mucosal injuries. However, despite the V45 value not being the highest, Patient B showed the most severe mucosal damage and higher Lewis score than Patients A and C. This may have been because the BMI of Patient B was low and there was little fat tissue around the pancreas, and the third part of the duodenum was closer to the center of irradiation than in Patient C.

The entire circumference of the proximal jejunum was included within the radiation field, because tumors of the pancreatic head move less in the craniocaudal direction than the anterior-to-posterior or left-to-right direction. Therefore, the safety margin of the radiation field was greater in the craniocaudal direction.

.

Reducing the symptoms of acute RE requires paying attention to the radiation dose and irradiation field in the small intestine, and the use of concurrent chemotherapy. Intraoperative radiotherapy, which has been used alone or in conjunction with external beam RT, can also help reduce RE[4], because it is aimed directly at the tumor during surgery, thus avoiding surrounding normal tissues.

The most serious complication of CE is capsule retention, which is caused by strictures of the intestinal lumen. Usually, strictures due to RE occur 8–12 months after RT, and Kim et al. reported that CE may be able to diagnose acute RE safely[2]. In our study, CE findings did not reveal any strictures and CE reached the cecum in all three cases without delay, thus, CE may be useful in diagnosing acute RE. Double balloon enteroscopy can also evaluate radiation jejunitis effectively and safely[5]. However, insertion of the enteroscope is difficult because of the edematous effect of RT, and there is the potential for exacerbating radiation-induced duodenitis and proximal jejunitis. Although computed tomography enterography, magnetic resonance enterography and the biomarkers such as calprotectin or lactoferrin are non-invasive diagnostic tools to evaluate RE, the data on these remain inconclusive[6].

In conclusion, this case series shows that CE can safely diagnose acute duodenitis and proximal jejunitis caused by CRT for ULAPC, and the dose distribution is possible to predict the degree of duodenal and jejunal mucosal injuries.

**Acknowledgments**

The authors thank all endoscopists who participated in the study and I express my appreciation to Mina Yamashina, for hearty encouragement and unconditional support.

**References**

1. Tempero MA, Malafa MP, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2014. *J Natl Compr Canc Netw* 2014; 12: 1083–1093.

2. Kim HM1, Kim YJ, Kim HJ,et al. A Pilot Study of Capsule Endoscopy for the Diagnosis of Radiation Enteritis. *Hepatogastroenterology*. 2011;58:459-464.

3. Classen J, Belka C, Paulsen F, et al. Radiation-induced gastrointestinal toxicity. Pathophysiology, approaches to treatment and prophylaxis. *Strahlenther Onkol* 1998; 174 Suppl: 82–84.

4. Nishioka A, Ogawa Y, Miyatake K, et al. Safety and efficacy of image-guided enzyme-targeting radiosensitization and intraoperative radiotherapy for locally advanced unresectable pancreatic cancer. *Oncol Lett* 2014; 8: 404–408.

5. Yamamoto H, Yano T, Ohmiya N, et al. Double-balloon endoscopy is safe and effective for the diagnosis and treatment of small-bowel disorders: prospective multicenter study carried out by expert and non-expert endoscopists in Japan. *Dig Endosc* 2015; 27: 331–337.

6. Harb AH, Abou Fadel C, Sharara AI. Radiation enteritis. *Curr Gastroenterol Rep* 2014; 16: 383.

**Table 1.** Characteristics of all three patients in this study

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Case | Age (years old) | PS  (ECOG) | Sex | Location of tumor | Radiation dose and fraction  (Gy/times) | Chemotherapy | Stage  (NCCN) |
| A | 60s | 0 | M | head | 50.4/28 | Gem 1000mg/m2 | T4N0M0 Stage3 |
| B | 70s | 0 | F | head | 50.4/28 | Gem 1000mg/m2  /nabPTX100mg/m2 | T4N0M0 Stage4 |
| C | 60s | 0 | M | head | 50.4/28 | Gem 1000mg/m2  /nabPTX100mg/m2 | T4N1M0  Stage3 |

COG, Eastern Cooperative Oncology Group; Gem, gemcitabine. NCCN, National Comprehensive Cancer Network; PS: performance status; PTX, paclitaxel.

**Table 2.** Body composition and biochemical markers of nutritional status before and 28 times after RT

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Case | Before  BMI | After  BMI | Before  WBC | After  WBC | Before  Hb | After  Hb | Before  Alb | After  Alb | Anorexia  (CTCAE) | Before  Lewis score | After  Lewis score |
| A | 17.7 | 18.1 | 4720 | 3600 | 13.9 | 12 | 3.8 | 3.5 | Grade 1 | 135 | 641 |
| B | 15.9 | 14.7 | 1790 | 1770 | 11.1 | 8.8 | 3.3 | 3.0 | Grade 2 | 0 | 4396 |
| C | 21.7 | 21.4 | 4110 | 3040 | 12.3 | 9.8 | 3.4 | 3 | Grade 2 | 370 | 782 |

Hb, hemoglobin; WBC, white blood cell.

**Table 3.** PTV, Dmax and V45 for duodenum

|  |  |  |  |
| --- | --- | --- | --- |
| Patient | PTV(cc) | Dmax(Gy) | V45(%) |
| A | 131 | 51.096 | 23 |
| B | 144 | 51.026 | 30 |
| C | 286 | 51.573 | 36 |

Dmax, maximum radiation dose of duodenum; V45: volume of the duodenum receiving ≥45 Gy

**Figure legends**

**Figure 1.** Yellow arrow indicates the beam setup for pancreatic head cancer. Red circle indicates the third part of duodenum. A: Patient A; B: Patient B; C: Patient C.

**Figure 2.** CE showing segmental mucosal erythema, edema, superficial erosions and narrowing intestinal tract in third part of duodenum. A: Patient A; B: Patient B; C: Patient C.