Annals of Gastroenterology (2016) **29,** 386-388

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

Takeshi Yamashina[a,e], Ryoji Takada[b], Noriya Uedo[a], Tomofumi Akasaka[a], Noboru Hanaoka[a], Yoji Takeuchi[a], Koji Higashino[a], Tatsuya Ioka[c], Ryu Ishihara[a], Teruki Teshima[d], Kinji Nishiyama[d], Hiroyasu Iishi[a]

Osaka Medical Center for Cancer and Cardiovascular Disease; Osaka Red Cross Hospital, Osaka, Japan

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 to examine the relationship between CE findings and dose distribution. CE after CRT 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 that dose distribution is possible to predict the degree of duodenal and jejunal mucosal injuries.

Keywords Radiation enteritis, capsule endoscopy, pancreatic cancer

Ann Gastroenterol 2016; 29 (3): 386-388

Introduction

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

Departments of [a]Gastrointestinal Oncology (Takeshi Yamashina, Noriya Uedo, Tomofumi Akasaka, Noboru Hanaoka, Yoji Takeuchi, Koji Higashino, Ruy Ishihara, Hiroyasu Iishi); [b]Pancreatic Oncology (Ryoji Takeda); [c]Cancer Survey (Tatsuya Ioka); [d]Radiation Oncology (Teruki Teshima, Kinji Nishiyama), Osaka Medical Center for Cancer and Cardiovascular Disease; [e]Gastroenterology and Hepatology, Osaka Red Cross Hospital (Takeshi Yamashina), Osaka, Japan

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

Correspondence to: Hiroyasu Iishi, MD, Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease, 1-3-3 Nakamichi, Higashinari-ku, Osaka 5378511, Japan, Tel.: +81 6 6972 1181, Fax: +81 6 6981 4067, e-mail: iisi-hi@mc.pref.osaka.jp

Received 13 November 2015; accepted 15 January 2016; published online 15 February 2016

DOI: http://dx.doi.org/10.20524/aog.2016.0063

Case reports

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 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/m^2 gemcitabine, and patients B and C received 1000 mg/m^2 gemcitabine plus 100 mg/m^2 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 included CTV with 5-mm margins (Fig. 1). During treatment, all three patients tried to avoid using non-steroidal anti-inflammatory drugs to prevent non-steroid anti-inflammatory drug-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 any 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 (Fig. 2). 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 (Figs. 1, 2). These findings were not seen by capsule endoscopy (CE) before CRT. There was no significant stenosis, and capsule retention did not occur. The Lewis scores after CRT in patients A, B and C were 641, 4396 and 782 respectively, and the scores were higher than before CRT in all three cases (Table 2). The percentage volumes of the duodenum receiving ≥45 Gy (V45) in patients A, B and C were 23, 30 and 36%, respectively (Table 3). During treatment, we observed anorexia (grades 1 or 2 according to CTCAE) in all three patients.

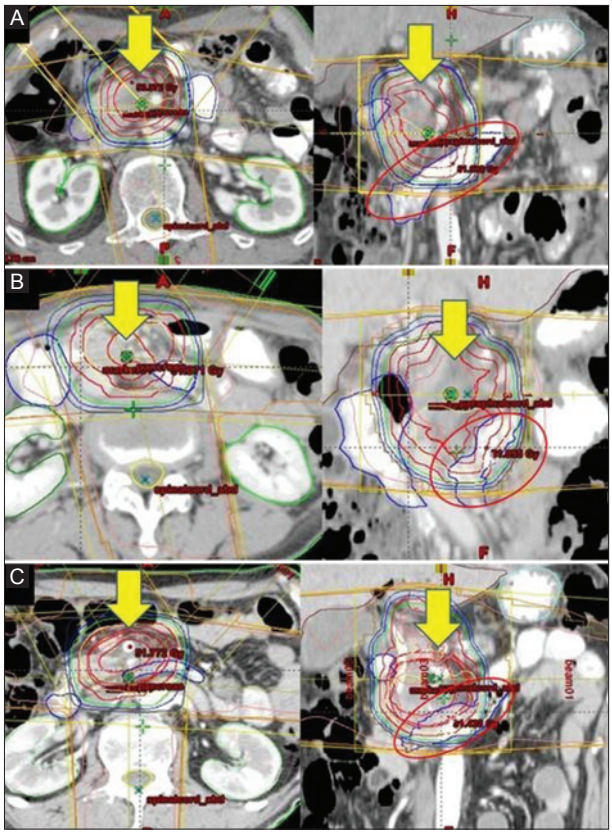

Figure 1 Yellow arrow indicates the beam setup for pancreatic head cancer. Red circle indicates the third part of duodenum. (A) Patient A; (B) Patient B; (C) Patient C

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 fact that the V45 value was not 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 body mass index of patient B was low and there was little fat tissue around the pancreas, and because 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.

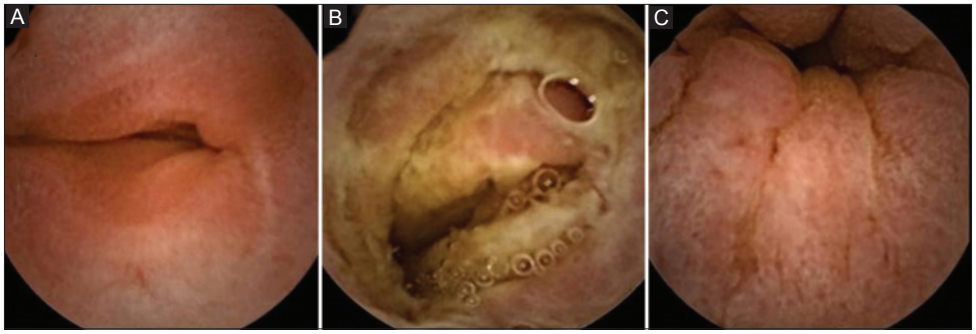

Figure 2 Capsule endoscopy showing segmental mucosal erythema, edema, superficial erosions and narrowing intestinal tract in third part of duodenum. (A) Patient A; (B) Patient B; (C) Patient C

Table 1 Characteristics of all three patients in this study

Case	Age (years)	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/m^2	T4N0M0 stage3
B	70s	0	F	Head	50.4/28	Gem 1000 mg/m^2/nab/PTX100 mg/m^2	T4N0M0 stage4
C	60s	0	M	Head	50.4/28	Gem 1000 mg/m^2/nab/PTX100 mg/m^2	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 radiotherapy (RT)

	Case		
	A	B	C
Baseline BMI (kg/m^2)	17.7	15.9	21.7
After RT BMI (kg/m^2)	18.1	14.7	21.4
Baseline WBC (×10^3/μL)	4720	1970	4110
After RT WBC (×10^3/μL)	3600	1770	3040
Baseline Hb (g/dL)	13.9	11.1	12.3
After RT Hb (g/dL)	12	8.8	9.8
Baseline Alb (g/dL)	3.8	3.3	3.4
After RT Alb (g/dL)	3.5	3.0	3
Anorexia (CTCAE)	Grade 1	Grade 2	Grade 2
Baseline Lewis score	135	0	370
After RT Lewis score	641	4396	782

Hb, hemoglobin; WBC, white blood cell; BMI, body mass index; Alb, albumin; CTCAE, Common Terminology Criteria for Adverse Events

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*; *PTV, planning target volume*

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 RT, 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, 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 Ms. Mina Yamashina for her 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 HM, 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.