



Endoscopic scoring of late gastrointestinal mucosal damage after adjuvant radiochemotherapy

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Received: 2005-11-29 Accepted: 2006-01-14

Gastroenterol 2006; 12(27): 4411-4415

<http://www.wjgnet.com/1007-9327/12/4411.asp>

Abstract

AIM: To evaluate late effects of chemoradiation on gastrointestinal mucosa with an endoscopic scoring system and compare it to a clinical scoring system.

METHODS: Twenty-four patients going to receive chemoradiation after gastric surgery underwent endoscopy four wk after surgery and one year after the chemoradiation finished. Upper gastrointestinal findings were recorded according to a system proposed by World Organisation for Digestive Endoscopy (OMED) and clinical scoring was done with RTOG-EORTC radiation morbidity scoring systems.

RESULTS: There was no significant endoscopic difference in gastric and intestinal mucosa after chemoradiation ($P > 0.05$) and there was no association between endoscopic scores and clinical scores. Endoscopic changes were minimal.

CONCLUSION: Late effects after chemoradiation in operated patients with gastric cancers can be evaluated with an endoscopic scoring system objectively and this system is superior to clinical scoring systems.

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Key words: Radiochemotherapy; Gastric cancer; Endoscopy; Gastrointestinal mucositis

Dabak R, Uygur-Bayramicli O, Gemici C, Yavuzer D, Sargin M, Yildirim M. Endoscopic scoring of late gastrointestinal mucosal damage after adjuvant radiochemotherapy. *World J*

INTRODUCTION

Irradiation of the gastric region has become popular in the setting of adjuvant treatment of resected high risk gastric cancer patients in recent years. It has been shown that adjuvant radiochemotherapy leads to a survival advantage in operated patients with gastric cancers^[1]. Gastrointestinal mucositis after radiation has been well studied especially in the oral cavity and oesophagus but chemotherapy induced gastrointestinal mucositis has been focused mainly on the small intestine^[2].

There is a lack of data about the mucositis of the stomach in the literature. Sartori *et al*^[3] reported gastric erosions after different chemotherapeutics but there is no study evaluating the effects of irradiation and chemotherapy on gastric and small intestinal mucosa and there is no standardised endoscopic scoring system to evaluate these effects. Ideally a mucositis scoring system should be objective, validated and reproducible across all clinical situations and applications. Because of the need of such a measurement instrument a number of different clinical scoring systems have been developed, most of them measuring oral mucositis (NCI-CTC, WHO, RTOG)^[4-6].

Endoscopy is considered to give the best estimation of gastrointestinal mucosal damage and is used extensively in the follow-up of operated gastrointestinal cancer patients. But there is no endoscopic evaluation or scoring system for chemoradiation induced gastrointestinal mucosal damage. Wachter *et al*^[7] proposed a scoring system for radiation induced proctitis based on the endoscopic terminology of the World Organisation for Digestive Endoscopy (OMED)^[8] and found it highly useful to show mucosal damage especially in asymptomatic patients (Table 1). Based on the study by Wachter *et al* we conducted the current research to evaluate the late effects of chemoradiation on gastrointestinal mucosa by using the terminology proposed by OMED.

MATERIALS AND METHODS

Patients

Between Jan 2001 and Jan 2005, a total of 102 patients received adjuvant chemoradiation for locally advanced

gastric adenocarcinoma (T3, T4 or nodal involvement) after operation at the Department of Radiation Oncology at Kartal State Hospital, Istanbul, Turkey. All these patients were invited to take part in the present study. Thirty-four of them accepted and gave informed consent.

Endoscopy was performed by the same experienced endoscopist at the Department of Gastroenterology in the presence of a resident who collected the data. It was done under standard conditions with a videogastroscope (Pentax 2980 type) 4 wk after the operation. Ten of 34 patients had total gastrectomy and esophagoenterostomy and were therefore excluded from the study. The remaining 24 comprised the study group and had a control endoscopy 1 year after the last day of radiation treatment.

In order to make a systematic description in patients who had a subtotal gastrectomy and any type of gastroenterostomy, the remaining stomach, stoma and 10-12 cm of intestine were examined endoscopically. The remaining stomach and the stoma was defined arbitrarily as part I representing the gastric mucosa and the intestinal tissue distal to the stoma as part II representing the intestinal mucosa.

Endoscopic findings were evaluated based on the terminology of OMED in both arbitrarily defined parts of examination separately.

Terminology of OMED as following:

-Telangiectasia:

- Grade 0: none
- Grade 1: single telangiectasia
- Grade 2: multiple non-confluent telangiectasia
- Grade 3: multiple confluent telangiectasia

-Congested mucosa:

- Grade 0: none
- Grade 1: focal reddening of the mucosa combined with an edematous mucosa
- Grade 2: diffuse not confluent reddening of the mucosa combined with an edematous mucosa
- Grade 3: diffuse confluent reddening of the mucosa combined with an edematous mucosa.

-Ulceration:

- Grade 0: none
- Grade 1: microulceration –superficial, < 1 cm²
- Grade 2: superficial > 1 cm²
- Grade 3: deep ulceration
- Grade 4: fistula, perforation

-Stricture:

- Grade 0: none
- Grade 1: > 2/3 of regular diameter
- Grade 2: 1/3 –2/3 of regular diameter
- Grade 3: < 1/3 regular diameter
- Grade 4: complete obstruction

-Necrosis:

- Grade 0: none
- Grade 1: necrosis

The highest grade of any one parameter qualified for the attribution to one of the given score levels regardless of the grade achieved in any other parameter. Pre and post treatment scores of the gastric and intestinal mucosa were compared.

Adjuvant treatment plan was similar to the intergroup study (INT- 0116) by MacDonald *et al*^[1]. Chemotherapy

Table 1 Endoscopy score system based on the system proposed by Wachter *et al*^[7]

	Congested mucosa	Telangiectasia	Ulceration	Stricture	Necrosis
Score 0	Grade 1	None	None	None	None
Score 1	Grade 2	Grade 1	None	None	None
Score 2	Grade 3	Grade 2	None	None	None
Score 3	Any	Grade 3	Grade 1	None	None
Score 4	Any	Any	Grade 2	Grade 1	None
Score 5	Any	Any	Grade > 3	Grade > 2	Any

Table 2 RTOG-EORTC late radiation morbidity scoring system (part for small/large intestine)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Small/large intestine	None	Mild diarrhea, mild ramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea and colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, fistula

(CT) either with bolus fluorouracil and leucovorin or with infusional fluorouracil was administered before, together and after radiation. CT (bolus fluorouracil 425 mg/m² and leucovorin 20 mg/m² for 5 d or infusional fluorouracil 1 g/m² for 5 d) was initiated on day 1 and followed by radiochemotherapy (RT) beginning 28 days after the start of the initial cycle of CT. Radiochemotherapy consisted of 46 Gy at 2 Gy per d, 5 d per wk, for five wk either with bolus fluorouracil (400 mg/m²) and leucovorin (20 mg /m³) or infusional fluorouracil (1 g/m³) on the first 4 d and last 3 d of radiation. The radiation field included the tumor bed, and regional lymphatics with the technic described by Smalley *et al*. Tumor bed was defined by preoperative computed tomography or barium roentgenography. Perigastric, celiac, hepatoduodenal or hepatic portal and pancreaticoduodenal lymph nodes were included in the radiation field. Treatment was delivered either with 6 or with 15 MV photons by anterior and posterior parallel opposed fields. Kidneys were spared with personalised blocks. The equivalent of at least two thirds of one kidney was spared from the radiation field. One month after the completion of radiotherapy, two cycles of CT either with bolus fluorouracil (425 mg/m²) and leucovorin (20 mg/m²) or infusional fluorouracil (1 gr/m³) for five days were given one month apart.

For each patient side effects of radiation were documented by use of EORTC/RTOG score at the end of one year and endoscopic findings were compared with small/large intestine items of the morbidity scale (Table 2).

Statistical analysis

Statistical analysis was performed with Pearson Chi-square test. *P* < 0.05 was considered significant.

Table 3 Posttreatment endoscopic scores for gastric mucosa and their correlation with RTOG-EORTC scores

Post treatment endoscopic scoring for gastric mucosa	RTOG-EORTC late radiation morbidity scoring (small/large intestine)				
	0	1	2	3	4
0 (n = 13)	5	3	5	0	0
1 (n = 9)	5	0	4	0	0
2 (n = 0)	0	0	0	0	0
3 (n = 0)	0	0	0	0	0
4 (n = 2)	0	1	1	0	0
5 (n = 0)	0	0	0	0	0

Table 4 Posttreatment endoscopic scores for intestinal mucosa and their correlation with RTOG-EORTC scores

Post treatment endoscopic scoring for intestinal mucosa	RTOG-EORTC late radiation morbidity scoring (small/large intestine)				
	0	1	2	3	4
0 (n = 19)	9	3	7	0	0
1 (n = 4)	1	1	2	0	0
2 (n = 0)	0	0	0	0	0
3 (n = 0)	0	0	0	0	0
4 (n = 1)	0	0	1	0	0
5 (n = 0)	0	0	0	0	0

RESULTS

All of 24 patients (7 females and 17 males) completed the study and there were no dropouts due to deaths, or interruption of CT or RT. Mean age of the patients was 50.79 ± 11.36 years (range 34-73 years).

There was no significant difference in total scores between pre and post treatment endoscopic findings in gastric and intestinal mucosa ($P > 0.05$). In a subgroup analysis there was only in congestion group a significant difference between pre and post treatment endoscopic findings for gastric mucosa ($P = 0.006$) and intestinal mucosa ($P = 0.02$) but not for other subgroups.

Post treatment endoscopic scores for gastric mucosa and their correlation with RTOG-EORTC scores are shown in Table 3. Overall 13 patients (54.2%) had no endoscopic finding at all but 3 (23 %) of them were scored as RTOG-EORTC grade 1 and 5 (38.5%) as grade 2. In addition, 9 patients had an endoscopy score of 1, but 5 were scored as RTOG-EORTC grade 0 and 4 as grade 2. Even in patients with an endoscopy score of 4 the RTOG-EORTC score was 1 or 2. These results showed that there was no correlation between endoscopic and clinical scorings for gastric mucosa.

Post treatment endoscopic scores for intestinal mucosa and their correlation with RTOG-EORTC scores are shown in Table 4. Overall 3 patients (15.8%) with an endoscopic score of 0 were scored as RTOG-EORTC grade 1 and 7 (36.8%) as grade 2 but 9 (47.4%) as 0. One of 4 patients with endoscopic score 1 had a clinical score of 0, another one had a score of 1 and 2 had a score of 2. There was no correlation between endoscopic scoring and RTOG-EORTC scores for intestinal mucosa.

DISCUSSION

The role of adjuvant treatment has been controversial until now in resected gastric cancers^[9-11]. Most of the adjuvant treatments consisted of chemotherapy with a number of phase III trials and three meta-analyses on this subject^[12,13]. Survival advantage with adjuvant chemotherapy is very minor according to these meta-analyses. A randomised trial from the British Stomach Cancer Group^[14] concerning adjuvant radiation alone failed to demonstrate a survival benefit although locoregional failures were decreased from 27% to 10.6%. The recent MacDonald^[1] trial combining adjuvant chemotherapy with radiation showed a major

survival advantage in comparison to only chemotherapy or radiation. In a recent trial by Ajani *et al*^[15] preoperative chemoradiotherapy increased curative resection rate, overall survival duration and disease-free survival duration. After these publications many centers accepted this chemoradiation treatment protocol as their standard therapy after surgical resection of gastric cancer. But the long-term side effects of these therapies on gastrointestinal mucosa have not been well studied. If we take the 5-year survival rate of 36% and the 3-year survival rate of 50% into consideration^[1], the early detection of side effects becomes even more important.

Gastrointestinal mucositis representing the injury to the gastrointestinal tract is becoming recognised increasingly as a toxicity with many chemotherapy regimens and radiation^[2]. It can be identified all over the alimentary tract. But there is little data in the literature concerning gastrointestinal mucositis especially gastric and intestinal mucositis^[16], whereas esophageal mucositis is the best studied one^[17-19]. There is one study by Sartori *et al*^[3] describing gastric erosions after chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil.

In order to assess gastrointestinal mucositis a scoring system is needed which should be objective, validated and reproducible across all clinical conditions. Because of these a number of different clinical scoring systems have been developed, the majority of them measuring oral mucositis like NCI-CTC, WHO, RTOG^[20]. There is no clinical scoring system specially designed for gastric or intestinal damage. The RTOG-EORTC scale measures the late radiation morbidity^[20]. Most of the clinical systems measure acute toxicity and not the permanent damage to the gastrointestinal mucosa. But Yeoh *et al* have shown that permanent damage occurs in 70%-90% of patients undergoing radiotherapy and because the patients treated for gastric or pelvic cancer constitute the majority of long-term cancer survivors the prevalence of chronic toxicity becomes more important^[21,22]. Moreover some patients may be asymptomatic but still have GI mucositis^[23,24].

Endoscopy is the gold standard of evaluating the gastrointestinal mucosa. Endoscopic scoring systems are very rare in the literature regarding the chemotherapy or radiotherapy induced injury to the alimentary tract. Sartori *et al*^[3] have conducted a randomized and placebo controlled study evaluating the misoprostol and omeprazole in the prevention of chemotherapy-induced acute gastroduodenal mucosal injury and used an arbitrary endoscopic

score system comprising erosions or ulcers in gastric or duodenal mucosa. They repeated the same study design later with omeprazole and ranitidine and found the score system a useful tool for the detection of gastroduodenal injury after CT^[25]. But both of these studies measured only acute effects (namely 7 d) of CT and did not measure the effects of radiation^[3,25].

Wachter *et al*^[7] conducted a study on late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma and used a six-scaled rectoscopy score for the evaluation of radiation induced proctitis. They concluded that for a valid and reliable correlation and comparison of radiation side effects an accurate objective tool like rectoscopy should be used. Chi *et al*^[26] have developed an endoscopic classification system of chronic radiation induced -proctopathy based on telangiectasia density and vascular coalescence. They found a good reproducibility rate among experienced endoscopists as well as gastroenterology fellows.

Based on these existing endoscopic scoring systems we planned to evaluate the late effects of chemoradiation on gastric and intestinal mucosa. Our study was unique because it evaluated the long-term (1 year) effects of both chemotherapy and radiation and it was not done on intact mucosa as the previous studies but after radical surgery.

The endoscopic score systems proposed by Sartori^[3] was not used because there were no items like stricture or necrosis representing long-term effects in their system. The system proposed by Wachter^[7] took all these parameters into consideration and was based on a terminology prepared by the OMED (World Gastroenterology Association). These terminologies are developed as the Minimal Standard Terminology for data processing in gastrointestinal endoscopy and used widely all over the world by gastroenterologists. Therefore we chose the system of Wachter which is proposed for radiation proctitis and evaluated this endoscopic scoring system on gastric and duodenal mucosa after chemoradiation for locally advanced gastric carcinomas with a resection before. The system was easy to use during routine endoscopy and easy for objective documentation. We could not find any significant difference in total scores between pre and post treatment endoscopic findings in gastric and intestinal mucosa. In a subgroup analysis there was only in congestion group a significant difference between pre and post treatment endoscopic findings for gastric and intestinal mucosa but not for other subgroups. Congestion is the first step in the mucosal damage and is mostly reversible. Therefore we can say that there was no significant chronic mucosal damage after chemoradiation and our endoscopic scoring system is a useful objective method to measure chronic damage. Our study also demonstrated that clinical scoring systems like RTOG-EORTC were not suitable to show gastrointestinal mucositis and there was no correlation between endoscopic and clinical scorings for gastric mucosa because the symptoms used in RTOG-EORTC might be caused by other physiological and individual factors. This observation was confirmed also by Wachter and Koc^[7,19]. Based on this disconnection between clinical and objective endoscopic scoring systems we propose to evaluate the chronic toxicity of chemoradiation with endoscopy and to decide discontinuation of therapy only after objective findings.

Endoscopic scoring systems are reliable and reproducible tools for the evaluation of gastric and duodenal mucosa after chemoradiation and might be of benefit because they show the gastrointestinal injury much more before it becomes clinically evident and give the best estimation of gastroduodenal mucositis in comparison to widely used clinical scoring systems where symptoms seem to be exaggerated due to multiple confounding variables.

In conclusion, there is no late gastroduodenal damage due to adjuvant chemoradiation in locally advanced gastric adenocarcinomas after operation.

ACKNOWLEDGEMENTS

We thank Semra Aktaş Kalaycı, MD, Can Dolapçioğlu, MD, Aygün Işık, RN, and Elvan Ermiş, RN for their support at the Endoscopy Department.

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S- Editor Wang J L- Editor Zhu LH E- Editor Liu Y