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**Quality of ulcer healing in** gastrointestinal  **tract: Its pathophysiology and clinical relevance**

Arakawa T *et al*. Quality of ulcer healing

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**Abstract**

In this paper we reviewed the concept of quality of ulcer healing (QOUH) in gastrointestinal (GI) tract and its role in the ulcer recurrence. In the past peptic ulcer disease (PUD) had been a chronic disease with life-cycle of repeated healing/remission and recurrence. The main etiologic factor of PUD is *Helicobacter pylori* (*H. pylori*), which is also the cause of ulcer recurrence. However, *H. pylori*-negative ulcer is present in 12-20% patients; they also recur and are on occasion intractable. QOUH is the concept which focuses on the fact that mucosal and submucosal structures within ulcer scar are incompletely regenerated. Within the scars of healed ulcers regenerated tissue is immature and with distorted architecture suggesting poor QOUH. The abnormalities in mucosal regeneration can be the basis for ulcer recurrence. Our studies showed that persistence of macrophages in the regenerated area plays a key role in the ulcer recurrence. Our studies in the rat model of ulcer recurrence indicates that pro-inflammatory cytokines trigger activation of macrophages, which in turn produce increased amounts of cytokines and chemokines, attract neutrophils to the regenerated area. Neutrophils release proteolysis enzymes that destroy the tissue resulting in ulcer recurrence. Another important factor in poor QOUH can be deficiency of endogenous prostaglandins and a deficiency and/or an imbalance of endogenous growth factors. Topically active mucosal protective and anti-ulcer drugs promote high QOUH and reduce inflammatory cells infiltration in the ulcer scar. In addition to PUD, the concept of QOUH is likely applicable to inflammatory bowel diseases including Crohn's disease and ulcerative colitis.

**Key words**: Quality of ulcer healing; Peptic ulcer disease; Recurrence; Prostaglandin; Cytokines; Growth factors

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**BIOGRAPHY**

Professor Tetsuo Arakawa （Figure 1） received his MD and PhD degrees from Osaka City University Graduate Medical School, Japan. He was Visiting Research Scholar and Professor at the University of California, Irvine (1990) and the University of Arizona, Tucson, AZ, USA (2000). He is currently Dean and Chairman, Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan. His CV lists 404 original articles, 421 review articles , 275 book chapters , 24 edited books, prestigious academic awards and honors and numerous presentations at national and international meetings, including American Gastroenterological Association (AGA), [**American College of Gastroenterology**](http://gi.org/) (ACG), Pasteur Institute and others (over 300 presentations). He has been President/Governor: Japanese Gastroenterological Association, Japanese Society of Gastrointestinal Endoscopy, Japanese Society of Ulcer Research, International Conference on Ulcer Research, Japanese Society of Neurogastroenterology, Japanese Society of Gastroenterological Immunology, and Japanese Society of Capsule Endoscopy chaired numerous sessions during American Gastroenterological Association Meetings and is member of 10 national/international societies, including Fellow of AGA and Fellow of ACG. His research interest covers numerous areas of gastroenterology, endoscopy and pathophysiology; he significantly contributed to the concept of cytoprotection, molecular mechanisms of gastric ulcer healing, mechanisms of anti-ulcer drugs action and translation of basic research to clinical application.

**INTRODUCTION**

Prior to the introduction of *Helicobacter pylori* (*H. pylori*) eradication treatment, peptic ulcer disease (PUD) had been a chronic disease affecting 5%-10% population with a life-cycle of repeated healing/remission and recurrence. The treatment aimed at eradication of *H. pylori* has changed the life cycle of this disease and the prevalence rate has dramatically decreased. However, the dictum “no *H. pylori*, no ulcer” is overrated[1]. *H. pylori*-negative PUD exists, similar as PUD in non-user of non-steroidal anti-inflammatory drugs (NSAIDs). This PUD is referred to as non-*H pylori*, non-NSAIDs ulcers or idiopathic PUD (IPUD)[2]. A prevalence rate of IPUD has been reported by 12%-20% suggesting that IPUD is not rare[2].A recent report has shown the increase in the prevalence of IPUD[3], however this remains controversial[4].

The recurrence rate of IPUD is higher than *H. pylori* and/or NSAID-associated PUD[5] and their management is more difficult and more costly compared to other ulcers[5]. The recurrence rate of ulcer may be related to quality of ulcer healing (QOUH). The pathogenesis of poor QOUH may be the underlying cause of the refractoriness and ulcer recurrence. In addition to PUD the concept of QOUH may be applicable to inflammatory bowel disease (IBD), which is also a chronic and recurrent ulcer disease. It is likely that in order to obtain a permanent ulcer healing and remission, the high QOUH is necessary for any type of ulcer disease.

**MYSTERY OF ULCER RECURRENCE: PAST HISTORY OF PATHOPHYSIOLOGY**

The ulcer recurrence has been thought for a long time to be a non-avoidable feature and a destiny of PUD, and therefore, the maintenance treatment had been necessary to prevent the recurrences. *H. pylori* was found to be a major cause of both PUD and the recurrences. The bacteria are, however, not the only cause of ulcer recurrence, and still there are a certain number of patients with PUD not related to *H. pylori* and NSAIDs, referred to as IPUD[2, 4]. To prevent recurrence of IPUD, the investigations examining the pathophysiology of ulcer recurrence are important.

Oi *et al*[6] have proposed the double-regulation theory to explain why PUD favors the place at gastric angle. They examined many operated stomachs with ulcer present and histologically characterized, and found that the ulcer site is usually at the interphase of distal side of glandular borderline (mucosal rule) and line of distortion of movement (muscular rule). This may be the point of combination of the mechanical tension and an exposure to high concentration of acid at pyloric gland area. The latter mucosa has a weaker resistance to acid compared to fundic gland area. This theory may also explain why the ulcer often recurs at the same or neighboring site of a previous ulcer. This theory, however, does not fit to duodenal ulcer or gastric ulcer at other sites. Therefore it is important to determine but how the ulcer recurs.

Pan *et al*[7] reported that the recurrence of healed duodenal ulcer depends on the histological maturity of regenerated mucosa. This report indicated that the cause of ulcer recurrence may be related to the abnormalities of scar of healed ulcer, leading to the concept of QOUH [7]. Okabe *et al* [8] have developed chronic gastric ulcer model in rats by topical application of acetic acid from the serosal side of gastric glandular borderline. This model closely mimics human PUD both in histology and life cycle of ulcer recurrence. Tarnawski *et al* [9] have demonstrated in this rat model that the subepithelial mucosa of macroscopically healed gastric ulcer displays disorganized restoration of glandular and vascular structures and remains histologically and ultrastructurally abnormal. They concluded that these abnormalities may interfere with oxygenation, nutrient supply, and with mucosal resistance and defense, and therefore could be the basis for ulcer recurrence. They proposed the concept of QOUH based on experimental ulcer model in 1990[9-11]. In a previous clinical study done by our group, we proposed the concept and definition of QOUH in human gastric ulcer in a Japanese journal, which has been published in English journal one and half years later[12] (Table 1). A flat or non-flat ulcer scar pattern has been defined with chromoendoscopy using indigo carmine, which was not demonstrated with conventional endoscopy (Figure 1). These patterns are compatible with histological maturity of regenerated mucosa at healed gastric ulcer; the flat pattern represents a good QOUH and non-flat represents poor QOUH[13] (Figure 1). The incidence of ulcer recurrence is much higher in a non-flat scar than in flat scar pattern[13, 14] (Figure 2), suggesting that the endoscopically assessed QOUH may detect scars that are predisposed to future ulcer recurrence.

**ULCER HEALING AND PROSTAGLANDINS**

Prostaglandins (PGs) and the discovery of phenomenon “cytoprotection” by Robert *et al*[15]. sparked an enormous interest in the critical role of PGs in mucosal defense and ulcer healing. In humans, "artificial" ulcers in GI tract produced by endoscopic mucosal resection for neoplasm heal rapidly and do not recur. We have shown that surrounding mucosa of such "artificial" ulcers synthesizes increased amount of PGE2 and prostacyclin[16], which may have a crucial roles in producing high QOUH. This observation lead to our contention that PUD may be a PG-deficiency disease[17] and that PG deficiency may cause poor QOUH. We have demonstrated that low-dose indomethacin causing PG-insufficiency condition makes an experimental chronic gastric ulcer heal with poor QOUH and that exogenous PGE2 reverses poor QOUH as assessed by recurrence rate after healing, and reduces inflammatory cell infiltration of ulcer scar[18] (Figure 3). Therefore, prostaglandin-derivatives and/or prostaglandin-inducing drugs such as mucosal protective compounds may promote high QOUH [19, 20].

Another important factor in poor QOUH can be a deficiency and/or an imbalance of endogenous growth factors. Jones *et al*[21] demonstrated that local gene therapy with vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang1), with limited duration of target gene expression, significantly accelerates experimental gastric ulcer healing in rats. Co-injection of both plasmids encoding rhVEGF 165 and rhAng1 resulted in formation of more mature vessels and more complete restoration of gastric glandular structures within the ulcer scar reflecting better QOUH. Inhibition of accelerated healing by a neutralizing anti-VEGF antibody indicates an essential role for VEGF and enhanced angiogenesis in ulcer healing.

**PATHOPHYSIOLOGY OF QOUH**

Histological evaluation of scars of healed gastric ulcers showed increased infiltration of regenerated tissue with numerous neutrophils and macrophages in a non-flat scar compared to flat scar (Figure 4). The persistence of chronic inflammation may be reflected by the finding of hypoechoic area beneath the ulcer scar with a non-flat pattern, assessed by endoscopic ultrasonography (Figure 5). The number of macrophages infiltrating scar tissue is five times higher than neutrophils in a non-flat scar, suggesting that these macrophages may play a key role in pathophysiology of QOUH and hence future ulcer recurrence. These macrophages produce increased amounts of interleukin-1 (IL1) beta, tumor necrosis factor (TNF)-, and monocyte chemotactic protein (MCP)-1 (Figure 6). The pro-inflammatory cytokines, IL-1beta and TNF-alpha further activate and stimulate macrophages, thus constituting a self-perpetuating circuit. The increased stimulation of these cytokines production induced by NSAIDs, stress, or *H. pylori* may cause these macrophages to increase cytokine production and/or release, leading in turn to attraction and accumulation of neutrophils. Neutrophils by releasing proteases and active oxygen species damage the scar tissue and induce ulcer recurrence.

**THE MECHANISMS UNDERLYING ULCER RECURRENCE**

As mentioned previously, Okabe’s rat model of chronic ulcer mimics human peptic ulcer not only morphologically and histologically but also in regard to life cycle of spontaneous recurrence. Numerous neutrophils and macrophages persist in and beneath the regenerated epithelium even after ulcer healing. This persistent chronic inflammation may have a key role in causing future ulcer recurrence. Watanabe *et al*[22] have demonstrated that inflammatory cytokines, IL-1 beta and TNF-alpha, administered systemically in rats with the macroscopically healed gastric ulcer cause ulcer recurrence at the site of previous ulcer (Figure 7). In this model of gastric ulcer recurrence, that we reported in 1997 we found increased expression of adhesion molecules, intercellular adhesion molecule 1 (ICAM-1) in endothelial cells and leukocytic beta2 integrins, lymphocyte function-associated antigen (LFA-1; CD11a/CD18) and Mac-1 (CD11b/CD18) in leukocytes, and also of cytokines, IL1-beta and TNF-alpha[22], and chemokine, MCP-1[23]. This increase occured in the regenerated tissue of healed ulcer site (scar) twelve hours after injection of an inflammatory cytokine and was followed by a massive infiltration with macrophages and by infiltration with neutrophils, ultimately resulting in ulcer recurrence. Anti-neutrophil antiserum prevented ulcer recurrence in this model, suggesting that neutrophils (producing noxious protease and active oxygen species) are the final mediator of tissue injury[22]. This hypothesis is further supported by demonstration that antibodies against adhesion molecules ICAM-1 and LFA-1 also inhibit ulcer recurrence[22]. These molecules regulate migration of neutrophils from arterioles into interstitial space. Antibody against MCP-1 prevents gastric ulcer recurrence in this model[23], suggesting that the overexpression of MCP-1 in resident macrophages accumulated in interstitial space of ulcer scar is a first step in the mechanism of ulcer recurrence because neutrophils and macrophages infiltrate the interstitial space of ulcer scar only after overexpression of MCP-1[24]. Proton-pump inhibitors (PPI) prevent gastric ulcer recurrence caused by injection of IL1-beta[24] and administration of exogenous acid reverses the protective action of PPIs on ulcer recurrence, suggesting that presence of acid is necessary to induce ulcer recurrence [24]. Based on these studies we proposed a working hypothesis of gastric ulcer recurrence presented in Figure 8[25].

**EFFECT OF ANTIULCER DRUGS ON QOUH**

The histological maturity of regenerated mucosa is poor after treatment with H2-receptor antagonists[26]. This may be related to its action to decrease mucosal prostaglandin levels[27]. Rebamipide, a mucosal protective drug stimulate synthesis of prostaglandins, accelerates ulcer healing and reduces relapse of acetic acid-induced gastric ulcer in rats. In contrast the ulcer relapse was not prevented by cimetidine[26]. Similar results regarding improving QOUH by rebamipide were reported by Qi *et al*[28]. In a clinical setting rebamipide was shown to improve QOUH of human gastric ulcers as assessed by chromo endoscopy. Moreover, the ulcer recurrence rate after healing with rebamipide was similar to that found in gastric ulcer patients after *H. pylori* eradication with dual therapy[29]. Rebamipide has been shown to exert anti-inflammatory action, accelerate gastric ulcer healing, and promote high QOUH in both in experimental and clinical studies [30, 31].

Regarding other drugs' action related to QOUH, antacid hydrotalcite provided better restoration of glandular structures in the gastric ulcer scar in rats compared to omeprazole[32]. In clinical studies, initial treatment with sucralfate is superior to cimetidine in decreasing recurrence rate of healed duodenal ulcer during maintenance therapy with cimetidine[33]. A direct evidence of promoting better QOUH, as assessed chromo endoscopy, has been reported with lafutidine in placebo-controlled trial and ranitidine compared to famotidine in patients with gastric ulcer[34,35]. Lafutidine is a novel H2-receptor antagonist developed in Japan. It has a unique property to stimulate capsaicin sensitive nerves producing nitric oxide, a cytoprotective mediator.

**RECENT ADVANCES IN EVALUATION OF QOUH**

Recent preliminary findings with magnifying endoscopy and narrow band imaging (NBI) may be useful for a more precise evaluation of QOUH. Magnifying endoscopy shows a fine regular glandular pattern in flat scar and coarse, Irregular, and hyperemic glandular pattern in non-flat scar (Figure 9), suggesting that a more precise assessment is possible in a near future. In addition to this procedure, NBI may be the most promising tool to assess QOUH combined with magnification because NBI shows pattern of vessels, which may reflect QOUH (Figure 10).

**MUCOSAL HEALING IN CROHN’S DISEASE**

Biological drugs aimed at TNF alpha such as infliximab (and other related antibodies) as well as thalidomide (36) promote ulcer healing in Crohn’s disease resistant to corticosteroids. This action is completely different from the mucosal healing obtained with a PPI for gastric and/or duodenal ulcers, because a PPI inhibits only acid secretion, but may not suppress inflammation. Therefore, a PPI promote rapid healing of acid-related ulcers, but does not improve QOUH, especially in presence of *H. pylori*. The biological drugs directly suppress inflammation, and thus they may improve QOUH. However, as long as responsible factor causing inflammation is unknown, the efficacy of such drugs may be limited.

Granulomas beneath the regenerated tissue may have important role in cell-to-cell contact of macrophages with T lymphocytes in Crohn’s disease and cause chronic inflammation, and on this background poor QOUH[37,38]. The inflammation in Crohn’s disease in based on Th1 and Th17 reaction [39-41] that is similar to *H. pylori*-associated gastritis[42,43]. Therefore, the inflammation in Crohn’s disease may have similar immune pathophysiology as *H. pylori*-associated inflammation, which causes poor QOUH and underlies the ulcer recurrence. The similarity of immunological abnormality in Crohn’s disease and *H. pylori*-associated gastritis may also be related to disturbance of ghrelin system [44,45].

In our preliminary study of 21 patients with Crohn’s disease treated with infliximab, morphological characteristics of active ulcer was defined, namely shape of ulcer edge; flat or non-flat, fold convergence; negative or positive, shape of ulcer base; flat or non-flat, stenosis; negative or positive, neighboring ulcer; negative or positive, width of ulcer; narrow or wide (Figure 11). The incidence of mucosal healing of active ulcer with flat ulcer edge, absence of neighboring ulcer, or a narrow width of ulcer is significantly higher. A negative mucosal fold convergence tends to be higher than that of non-flat ulcer edge, positive fold convergence, positive neighboring ulcer, or wide width of ulcer (Table 2). The latter type of ulcer may require a stronger anti-inflammatory treatment to obtain mucosal healing. These ulcers may need an endoscopic follow-up observation with assessment of mucosal healing after remission. If the ulcer does not recur, the mucosal healing may be high QOUH. Mucosal fold convergence (Figure 11C) may be one of the factors reflecting poor QOUH. Therefore, prevention of the convergence may improve QOUH of Crohn’s disease. Stimulation of the local angiotensin II system may have a key role in fibrosis resulting in fold convergence and stricture[46], suggesting that inhibitors on this system such as angiotensin II receptor blockers may promote high QOUH in Crohn’s disease. However, to identify a causative factor of inflammation in Crohn’s disease is the most essential. The responsible antigen needs to be elucidated from candidates such as yeast-like antigen[47], and others. Elimination of the possible antigen may be the powerful tool to obtain high QOUH and permanent remission.

The concept and the paradigm of QOUH may also apply to ulcerative colitis. Tarnawski and coworkers using confocal endomicroscopy and molecular imaging demonstrated in colonic mucosa of patients with ulcerative colitis in remission impaired crypt regeneration, persistent inflammation, pathological angiogenesis and increased microvascular permeability, all reflecting impaired QOUH. They found that the underlying mechanisms include dysregulation of survivin, aberrant activation of VEGF gene and persistent inflammatory cell infiltration [48].

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**Figure 2 Assessment of endoscopic** quality of ulcer healing. Flat pattern (a) and non-flat pattern (b) are identified by chromoendoscopy, but not by conventional endoscopy. Flat pattern reflects good quality of healing compared to nodular pattern as assessed by histological maturity (Arakawa T and Kobayashi K. *Gastroenterol Jpn* 1993[12] ).

**Figure 3 Cumulative remission rates of healed gastric ulcers with flat pattern and non-flat pattern.** The incidence of ulcer recurrence is much higher in the ulcer scar with a non-flat pattern than flat pattern (Nebiki H *et al*. *J Gastroenterol Hepatol* 1997 [14]).

**Figure** 4 **Effect of low dose indomethacin given during initial period of healing process of gastric ulcer induced by application of acetic acid in rats on cumulative remission rate after healing and on neutrophil infiltration of interstitial space of ulcer scar.** Indomethacin treatment enhances neutrophil infiltration and this phenomenon persists even after cessation of this drug. Concomitant administration of 16, 16-dimethyl prostaglandin E2 with indomethacin reverses these effects by indomethacin. a. Cumulative remission rate after healing. b. Infiltration with polymorphonuclear (PMN) cells during and after healing. control; indomethacin; indomethacin + 16, 16-dimethyl prostaglandin E2 (Arakawa T *et al*. *Dig Dis Sci* 1996 [18]) .



**Figure 5 Number of inflamatory cells infiltrating interstitial space of ulcer scar with flat pattern or non-flat pattern assessed by chromoendoscopy in patients with macroscopically healed gastric ulcer.** The number of neutrophils and macrophages is much higher in non-flat scar than in flat pattern. The number of macrophages is increased five times vs.neutrophils in non-flat scar. *N* = 6, b*P* < 0.01.

**Figure 6 Assessment of interstitial space beneath gastric ulcer scar with endoscopic ultrasonography.** Hypoechoic area (circle of red line) is clearly seen in non-flat scar (b), but not in flat scar (a). Yellow arrow shows a point of ulcer scar (Nebiki H *et al*. *J Gastroenterol Hepatol* 1997 [14]).

**Figure 7 Number of TNF-****, IL-1****, and MCP-1 producing cells in interstitial space of ulcer scar site in patients with gastric ulcer whose ulcer healed with flat vs. non-flat pattern assessed by chromoendoscopy.** *N* = 6, b*P*< 0.01.

**Figure 8 Original rat model of gastric ulcer recurrence.** a. Ulcer scar of acetic acid-induced gastric ulcer healed spontaneously (big arrow) with fold convergence (small arrows). b. Recurrence of ulcer with white coat at the same site of previous ulcer existed (big arrow). IL-1 or TNF- administered systemically causes recurrence of ulcer macroscopically and histologically. Anti-neutrophil antiserum, antibodies against adhesion molecules, antibody against MCP-1, or proton-pump inhibitors prevent the recurrence. MCP-1 is overexpressed in macrophages being interstitial space of ulcer scar site at 12 hours after administration of IL-1beta or TNF-alpha. Then adhesion molecules are overexpressed only at the ulcer scar site (Watanabe T *et al*. *Am J Pathol* 1977 [22]; Watanabe T *et al*. *Am J Physiol* 2004 [23]; Watanabe T *et al*. *Gut* 2001 [24]).

**Figure 9 Proposed mechanisms of ulcer recurrence.** Ulcerogenic factors such as non-steroidal anti-inflammatory drugs , stress, and *Helicobacter pylori* stimulate the production of inflammatory cytokines, which activate macrophages under the acidic condition. The activated macrophages produce MCP-1, which accumulates other macrophages. These macrophages all together produce much amount of IL-1 and TNF-, which activate cytokine network, resulting in activation of adhesion molecules and neutrophils. Then activated neutrophils migrate from arterioles to interstitial space and injure the tissue with noxious substance such as active oxgen species and elastase produced by themselves together with gastric acid (Arakawa T *et al*. *Dig Dis Sci* 1998 [25]).

**Figure 10** **Magnifying chromoendoscopy shows different findings in flat scar as fine regular pattern** (A) and non-flat scar as coarse irregular pattern (B) compatible with histological findings.

**Figure 11** **Narrow band imaging with magnification by endoscopy in patients with gastric ulcer shows fine vascular patterns, which may reflect precise** quality of ulcer healing **.** A: Conventional endoscopy; B: Magnifying endoscopy; C: Magnfiication + narrow band imaging .

**Figure 12** **Morphorogical characteristics of active ulcer in patients with Crohn’s disease.** Shape of ulcer edge; flat (a) or non-flat (b), fold convergence; negative or positive (c), shape of ulcer base; flat (d) or non-flat (e), stenosis; negative or positive (f), neighboring ulcer; negative (g) or positive (h), width of ulcer; narrow (i) or wide (j).

**Table 1 Definition and criteria of quality of ulcer healing**

|  |
| --- |
| **Definition**: **quality of ulcer healing (QOUH)** represents histological maturity of healed peptic ulcer. Evaluation of QOUH should be done to assess functional and endoscopic maturity additionally to histological matuirty. For a clinical use an endoscopic evaluation of maturity should be the main method.**Criteia**:  |
| 1. Endoscopic evaluation of maturity

Dye-contrast method, magnified endoscopy, endoscopic ultrasonography.1. Histological maturity

Regenerated mucosa: thickness, width, morphorogical abnormalities of glands, inflammatory cell infiltration.Granulation tissue: angiogenesis, fibroblasts and fibrosis, regeneration of muscularis mucosae, inflammatory cell infiltration.1. Functional evaluation of maturity

Microcirculation, production of mucin, prostanoids, growth factors, cell proliferation, receptor expression, adhesion molecules. |

 (Arakawa T, Kobayashi K. 1993[12 *Gastroenterol Jpn*)

**Table 2 Morphological characteristics of active ulcers in patients with Crohn’s disease reflecting possible future mucosal healing after treatment with infliximab**

 Mucosal healing

Morphological finding

 Good (*n* = 10) Poor (*n* = 11) *P*-value

Shape of ulcer edge Flat 8 3

 Non-flat 2 8 0.03

Fold convergence Negative 7 3

 Positive 3 8 0.08

Shape of ulcer base Flat 4 3

 Non-flat 6 8 0.65

Stenosis Negative 8 9

 Positive 2 2 0.99

Neighboring ulcer Negative 9 4

 Positive 1 7 0.02

Width of ulcer Narrow 9 4

 Wide 1 7 0.02

1Fisher's exact test. *P*-value indicates the statistical difference in morphological findings between good and poor mucosal healing.

