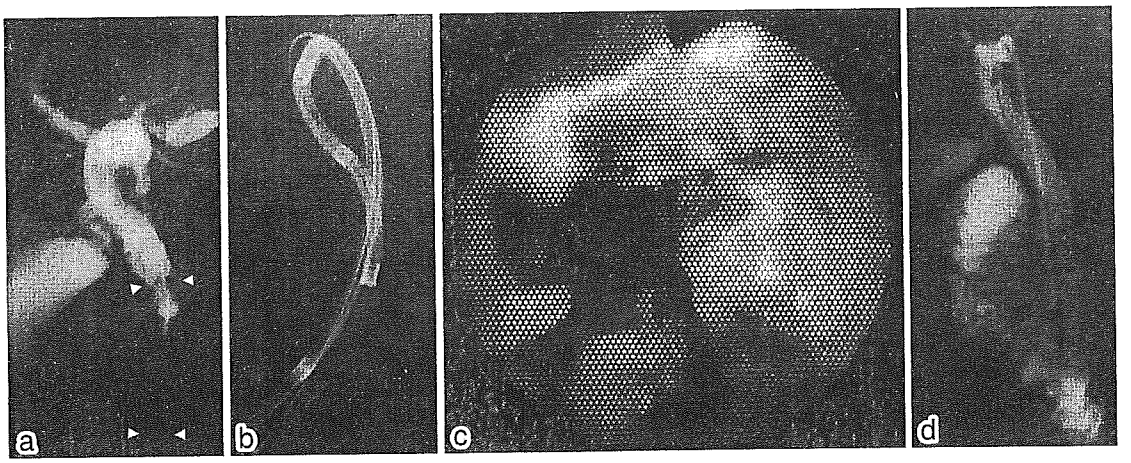

Figure 2. Metallic stent 閉塞の再開通：Recanalization of occluded metallic stent **a**：ステント閉塞時の胆道ドレナージからの胆管像；中部胆管癌．肝転移のため保存的治療が選択された．患者側の意向により放射線療法は施行されなかった．ステント挿入4カ月後に閉塞性黄疸を生じた．ステント挿入部に閉塞を認める(矢頭)． **b**：胆道鏡施行時のレントゲン像；初期の症例のため，閉塞部位の観察を行った． **c**：胆道鏡所見；易出血性の不整腫瘤がステント内腔に充満している．生検で癌と診断された． **d**：再開通時の胆道造影；腫瘍のステント内増殖に対してステントを追加（stent in stent）して開通が得られた．

られない．中下部胆管のステント閉塞にはNBDを行い，まず胆管像を得る．著明なtumor ingrowthにはステント追加を，軽度のtumor ingrowthに胆泥による閉塞をともなった状態にはバルーンカテーテル等を用いた内視鏡的クリーニングを行う．肝門部ステント閉塞に対しては，PTBDの方がステント追加，tumor ingrowthに対するマイクロ波治療等は施行しやすい[25]．NBD映像下PTBDの手技に熟知していれば，まずNBDを施行しその造影の結果でPTBDに変更する事もできる[9)10)]．ステントの専門家といわれるためには，胆道鏡等を用いてステント閉塞機序をきちんと検討した経験が必要である[32]．Uncovered metallic stent閉塞をすべてtumor ingrowthと考えるようではいけない．

おわりに

胆管癌の治療にはたくさんのオプションがあるため，入院早期から内科と外科が十分連絡をとり，患者の希望を十分取り入れて方針をたてるべきである．優れた診断法，治療法が早く保険適応になる事が望まれる．

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Case Report

A Case of Esophageal Stricture Due to Metastatic Breast Cancer Diagnosed by Endoscopic Mucosal Resection

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Metastasis of breast cancer to the esophagus has been reported but is rare. It is often difficult to diagnose metastases of breast cancer to the esophagus because they are often located in the submucosa and covered with normal mucosa. Although several methods have been reported in order to obtain specimens for pathological diagnosis, the adverse effects including bleeding and perforation were considerable problems. We report a case of a patient with esophageal stricture due to metastatic breast cancer to the esophagus. Pathological diagnosis was successfully obtained using endoscopic mucosal resection of the esophagus.

Key words: tumor metastasis to esophagus – metastatic breast cancer – endoscopic mucosal resection

INTRODUCTION

Tumor metastasis to the esophagus is a rare occurrence, and breast cancer is its most frequent origin (1–3). Diagnosis of esophageal stricture resulting from metastatic breast cancer is often difficult, and most cases were diagnosed on autopsy and surgery (1,4–10). Only some cases have been reported in which endoscopic biopsy confirmed metastatic breast cancer of the esophagus (1,4–10).

We present here a case of a patient with esophageal stricture due to metastatic breast cancer of the esophagus, in whom pathological diagnosis was successfully established using endoscopic mucosal resection (EMR) of the esophagus.

CASE REPORT

A 68-year-old woman was admitted to our hospital because of increasing symptoms of dysphagia lasting several years. She had had a mastectomy due to breast cancer when she was 45 years old. Upper endoscopy showed a severe stricture in the mid-esophagus where the endoscope could not pass through (Fig. 1). Repeated biopsy from the stricture was negative for malignancy. Chest computed tomograpy (CT) showed thickening of the wall of the esophagus around the stricture (Fig. 2). Endoscopic ultrasound (EUS) of the stricture revealed thickening of the fourth layer around the esophagus (Fig. 3). Laboratory data revealed a normal level of CEA (3.2 U/ml), and an elevated level of CA15-3 (52 U/ml). After receiving informed consent, the stricture was dilated endoscopically using a balloon dilator. The esophageal mucosa covering the lumen of the stricture after the dilation was smooth and neoplasm was not detected by another repeated biopsy. We could not obtain the diagnosis for the stricture even after the dilation therapy, and the patients was carefully observed because her symptoms had disappeared and also she did not

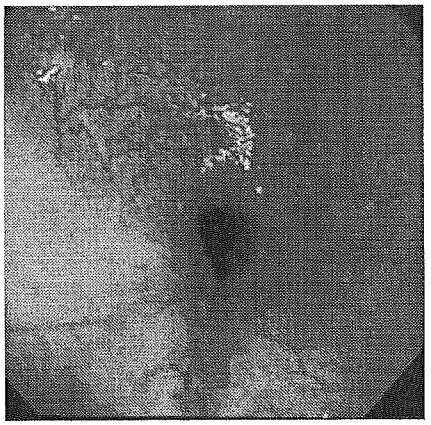

Figure 1. Endoscopic view of the esophageal stricture. The esophageal mucosa on the stricture appeared normal.

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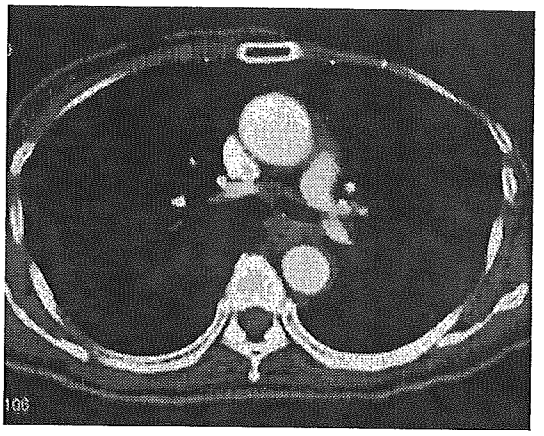

Figure 2. Chest computed tomography revealed thickening of the esophageal wall at the carina.

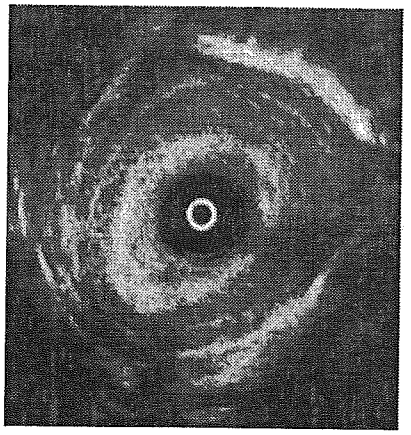

Figure 3. Endoscopic ultrasound of the stricture revealed the thickening of the fourth layer around the esophagus.

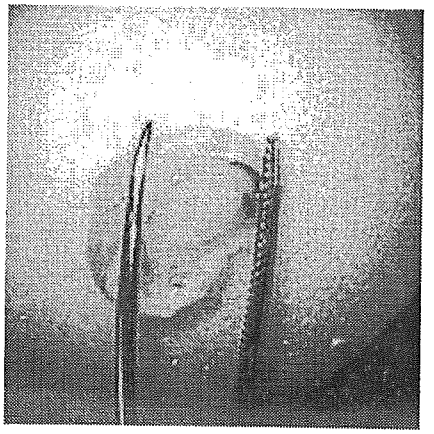

Figure 4. Macroscopic view of the resected specimen. The mass lesion was observed from the bottom.

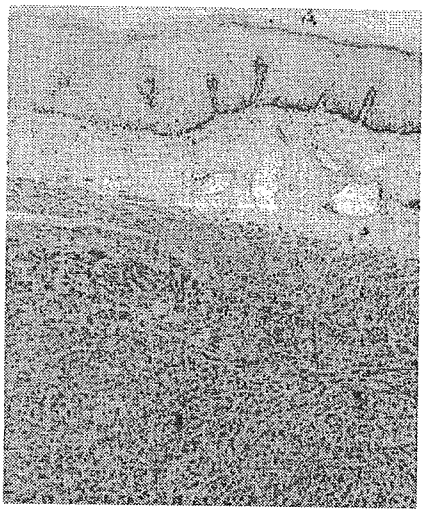

Figure 5. Microscopic findings revealed adenocarcinoma beneath the mucosa.

want further study at that time. However, she had dysphagia 6 months later and was again admitted to our hospital. Esophagoscopy on admission demonstrated a similar esophageal stricture at the same location. In order to make a pathological diagnosis, EMR was carried out for the stricture lesion using a cap method after the injection of 20 ml of saline underneath the mucosa (Fig. 4) (11). There were no complications including perforation and bleeding after EMR. The pathological diagnosis was adenocarcinoma (Fig. 5). Immunostaining of the resected sample was positive for Her-2, ER, PgR, GCDFP and CAM 5.2. Although detailed information on the original breast cancer was not available because the operation had been done >20 years previously, these results strongly indicate that the stricture was due to metastasis from the breast cancer. After the diagnosis, she was treated with hormone therapy. She gained weight after 6 months of treatment, and she had no symptoms during the 8 months of follow-up.

DISCUSSION

Since the first reported case of metastatic esophageal carcinoma from the prostate in 1942 (12), a wide variety of metastatic esophageal tumors have been reported from various organs, including breast, larynx, thyroid, hypopharynx and stomach (7,13,14). Breast carcinoma represents one of the most frequent origins of metastasis in the esophagus (1–3). Diagnosis of breast cancer metastasis to the esophagus is difficult, and esophageal involvement can occur without clinical symptoms in a considerable number of patients with breast cancer. Abrahms et al. reported seven patients with esophageal metastases on autopsy among 167 patients who died of breast cancer (15). Asch et al. also performed an autopsy series of 337 patients who died of breast cancer and found 20 patients

with esophageal metastases, although dysphagia was present in only two of them (16). Graham et al. suggested a prevalence of up to 6% of metastases in the esophagus for breast cancer, although clinically symptomatic cases would not be as numerous (17). The mechanism of esophageal spread from breast cancer has been controversial. Involvement of periesophageal lymph nodes through intra-mammary lymphatic channels was suggested to cause esophageal obstruction usually at the level of the carina (18,19).

Dysphagia is one of the most common clinical presentations associated with esophageal metastasis from breast cancer. The mean period between the diagnosis of cancer and the onset of symptoms due to esophageal metastases was reported to be ~8 years, including the previously recorded longest time interval of 22 years (17). In our case, ~20 years had passed to the onset of dysphagia due to esophageal metastases after the first diagnosis of breast cancer was made.

Metastatic esophageal carcinoma is a diagnostic challenge because of the difficulty of obtaining adequate specimens for pathological diagnosis. It is also difficult to differentiate it from primary esophageal carcinoma. In our case, esophagoscopy exhibited a stricture with normal mucosa, which was a typical macroscopic feature of the metastatic esophageal carcinoma. Biopsy from the stricture is often negative. Anderson et al. reported 15 cases of secondary esophageal tumor diagnosed from an autopsy and surgical pathology, including seven cases of lung cancer, four cases of breast cancer and single cases of kidney, pancreas and cervical cancers (20). Laforet et al. reported that biopsy was performed endoscopically in seven patients with esophageal strictures due to secondary esophageal tumor and accompanied with three perforations, while diagnostic tissue was recovered in three cases (21). Varanasi et al. reported that of three cases of breast carcinoma metastatic to the esophagus, diagnosis was made by surgery in two cases and by lymph node biopsy in one case (4). Esophageal obstruction was also observed in mediastinal metastasis from breast cancer (10,22).

Several techniques have been introduced for the diagnoses of strictures with possible involvement of either primary or metastatic neoplasms. Wiersema et al. and Giovannini et al. separately described the combination of EUS and EUS-guided fine-needle aspiration as a diagnostic method to treat submucosal tumor (SMT) (23,24). However, the relatively small specimens obtained with this method make it difficult to differentiate benign from malignant tumors. Normal findings also do not exclude the possibility of malignancy, (25,26). The guillotine needle biopsy technique described by Caletti et al. is safe, but up to three consecutive procedures are required for histological confirmation (27). Large forces in conjunction with a tunneling technique can be used to obtain sufficient samples. However, bleeding may be troublesome as a complication of this technique (28,29).

EMR is a widespread technique of cutting mucosal lesions through the submucosa (30). EMR is also applicable to treat SMT in the esophagus and stomach, although indications for endoscopic treatment of SMT have not been established (31,32). Several EMR techniques have been developed for the diagnosis of SMT. Takahashi et al. and Yu et al. separately reported that EMR is a safe method for obtaining tissues for histological diagnosis (18,19). Kawamoto et al. found that endoscopic submucosal tumorectomy was useful, but this technique should be restricted to the lesions limited to the submucosa (33). In this patient, we have applied the EMR technique for the diagnosis of the occupying lesion in the esophagus presumably located in the submucosa. The diagnosis was of clinical importance because metastasis from breast cancer can be treated by chemotherapy, radiotherapy and/or hormone therapy.

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H. pylori 除菌と消化性潰瘍・関連疾患

—基礎・臨床研究のアップデート—

I. 総　　説

「EBMに基づく胃潰瘍診療ガイドライン」作成の意義

菅野健太郎

I. 総　　説

「EBMに基づく胃潰瘍診療ガイドライン」作成の意義

Significance of the Japanese guideline for the management of gastric ulcer

菅野健太郎

Key words：clinical guideline, evidence-based medicine, gastric ulcer, *Helicobacter pylori*, NSAID

はじめに

平成12年度から2年間の厚生労働省の研究助成を受けて作成された胃潰瘍診療ガイドラインが一般向けの書籍として公表され[1]，2004年から医師向け，2005年から一般国民向けにもインターネット上で公開された[2]．このガイドラインは，従来の専門家による診療指針とは基本的に異なり，2001年までの約20年間のエビデンスを体系的に収集，分析を行うというEBMの手法に基づいて作成されるとともに，成因論的な治療体系の整理，医療経済的考察，患者を治療計画の重要な参画者として位置づけ患者向けの解説を加えることなど，従来の指針にない新しい特色をもっている．

本稿ではEBMに基づく胃潰瘍診療ガイドラインの意義と問題点，今後の方向性について解説することとしたい．なお本ガイドラインの詳細については書籍ならびにインターネット上で公開されているガイドラインを参照いただきたい．

1. Evidence-based medicine (EBM) と胃潰瘍診療ガイドライン

EBMを実践するためには体系的な文献収集やその客観的な評価が欠かせない．そのためには，体系的かつ再現性を保証する方法論，すなわち文献検索の手法を明示し，収集した文献の質的な評価方式をあらかじめ提示することによって，エビデンスとして採用する文献の信頼性と再現性を高めることが求められる．今回のガイドライン作成にあたっては，①文献データベース(Medline，医学中央雑誌などを限定)と検索範囲を過去20年間と定め，それを一定の文献検索式に従って検索すること，②得られた文献を一定の基準に従って質的な評価を行うとともにそのデータベースを公表すること，③質的評価の高い文献的エビデンスに基づき，治療上の有効性，費用や副作用などを考慮して治療勧告を行うという手法を採用した．ただ，臨床上のすべての問題点に対して文献的エビデンスが必ずしも存在するわけではないし，たとえエビデンスがあってもそれはしばしば一定の制約に基づいた臨床試験から得られた最大公約数的結果であって，個別の患者や医療機関のいかんにかかわらず一律に適応可能なものではない．このようにEBMに基づくガイドラインには自ずと一定の制約があり，したがってその指針を一律にすべての患者に適応すべきではないし，当然のことながら医師の裁量権や患者の自由意思を犯すものであってはならない．しかし，一方で，ガイドラインを明示することによって，恣意的な診療や根拠のない診療に対する一定の歯止めとなることが期待されるのである．

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2. 胃潰瘍診療ガイドラインの概要

図1に今回作成した胃潰瘍診療の流れを示すフローチャートの概略を示す．このフローチャートは，潰瘍出血の有無を出発点とし，胃潰瘍からの出血に対する内視鏡治療適応を定めている．胃潰瘍出血では，噴出性，湧出性を問わず活動性の出血を認める場合（Forrest分類Ia，Ib）と，検査時に止血されているものの潰瘍底に露出血管を認める場合（Forrest分類IIa）は，再出血リスクが高いため内視鏡的止血治療の適応となる．内視鏡止血に成功した場合には，再出血の抑制に有効であるとのエビデンスが示されているプロトンポンプ阻害薬（PPI）あるいはH_2受容体拮抗薬（H2RA）による酸分泌抑制療法を行う．一方，消化管出血を来した胃潰瘍でも，内視鏡検査時に上記（Forrest分類IIaまで）のハイリスク出血所見のない場合には内視鏡治療を行わず酸分泌抑制薬の投与を開始する方針を採用している．出血性胃潰瘍の内視鏡止血に成功し，それに引き続く酸分泌抑制薬治療によって潰瘍出血のリスクがなくなれば，非出血性の通常の胃潰瘍治療に準じた治療方針に移行する．

消化管出血に対する緊急内視鏡止血の場合には止血が最優先するので，潰瘍の成因論を考慮する必要はないが，通常の潰瘍治療においては，潰瘍の成因によって対応が異なるので，治療計画はその成因すなわち*H. pylori*感染，NSAID使用歴を考慮して行うことが求められる．*H. pylori*感染が陽性で，*H. pylori*除菌適応がある患者には除菌を行うことが勧められる．これは，除菌治療が潰瘍の治癒効果を高め，再発を抑制し，医療経済的にも優れているというエビデンスレベルの高い根拠が存在することによる．潰瘍のもう一つの重要な成因であるNSAID使用歴を確認するためにはきちんとした問診が重要である．NSAID使用歴が明白な場合には，その使用を中止することが最も合理的（原因除去）かつ効率的（薬剤費の削減，治療効果の向上）と考えられる．NSAIDを中止した場合には，非NSAID潰瘍に準じた状態といえるので，それ以降の診療の流れは通常潰瘍と同様，*H. pylori*陽性であれば除菌治療を，陰性であれば従来の潰瘍初期治療を行えばよい．一方，NSAIDを継続しなければならない場合には，*H. pylori*除菌治療により潰瘍治癒がむしろ遷延する可能性があることから除菌は治療選択とならず，PPIないしプロスタグランジン（PG）製剤による治療が最適である．NSAID潰瘍は医原性疾患の要素をもつため，予防も重要である．医師は，NSAIDを患者に処方する場合には，消化性潰瘍の副作用が起こり得ることを説明するとともに，ハイリスク患者に対しては予防処置を講じるべきであり，医療経済的に妥当性があるという外国のエビデンスも存在する．ガイドラインでも安全性の高いCOX-2選択的薬剤の使用，あるいはPPIや高用量のH2RAの継続使用などの予防を提唱しているが，現行の保険診療制度では実施困難なものが多い．

我が国では少数であるが，非*H. pylori*，非NSAID胃潰瘍あるいは，*H. pylori*陽性でも除菌適応のない潰瘍に対しては，酸分泌抑制薬による抗潰瘍治療を行う．抗潰瘍薬の選択にあたっては，当然のことながら単剤療法での有効性の高い薬剤が選択される．このため，PPIが第1選択薬として推奨された．H2RAも有効性が明確に示されているので推奨される．スクラルファートなどの一部を除く多くの防御因子製剤は，これらを上回る有効性を示すエビデンスが欠如しており，単剤療法の選択肢からは除外された．一方，我が国で多用されているPPIやH2RAと防御因子増強薬との併用療法は，その有用性を示す十分なエビデンスが不十分であり推奨されていない．更に潰瘍再発を防止するための維持療法については，除菌後の維持療法に関する文献的エビデンスがなく評価不可能であった．非除菌治療による通常潰瘍治療後については維持療法の効果を示す文献が認められたが，H2RAを中心とした限定された薬剤に限られており，スクラルファート以外の防御因子増強薬についてはエビデンスが欠如していた．いずれにせよこれらのエビデンスの多くは，*H. pylori*除菌治療が導入される以前のものであり，*H. pylori*陰性患者あるいは除菌後再発潰瘍に適した維持療

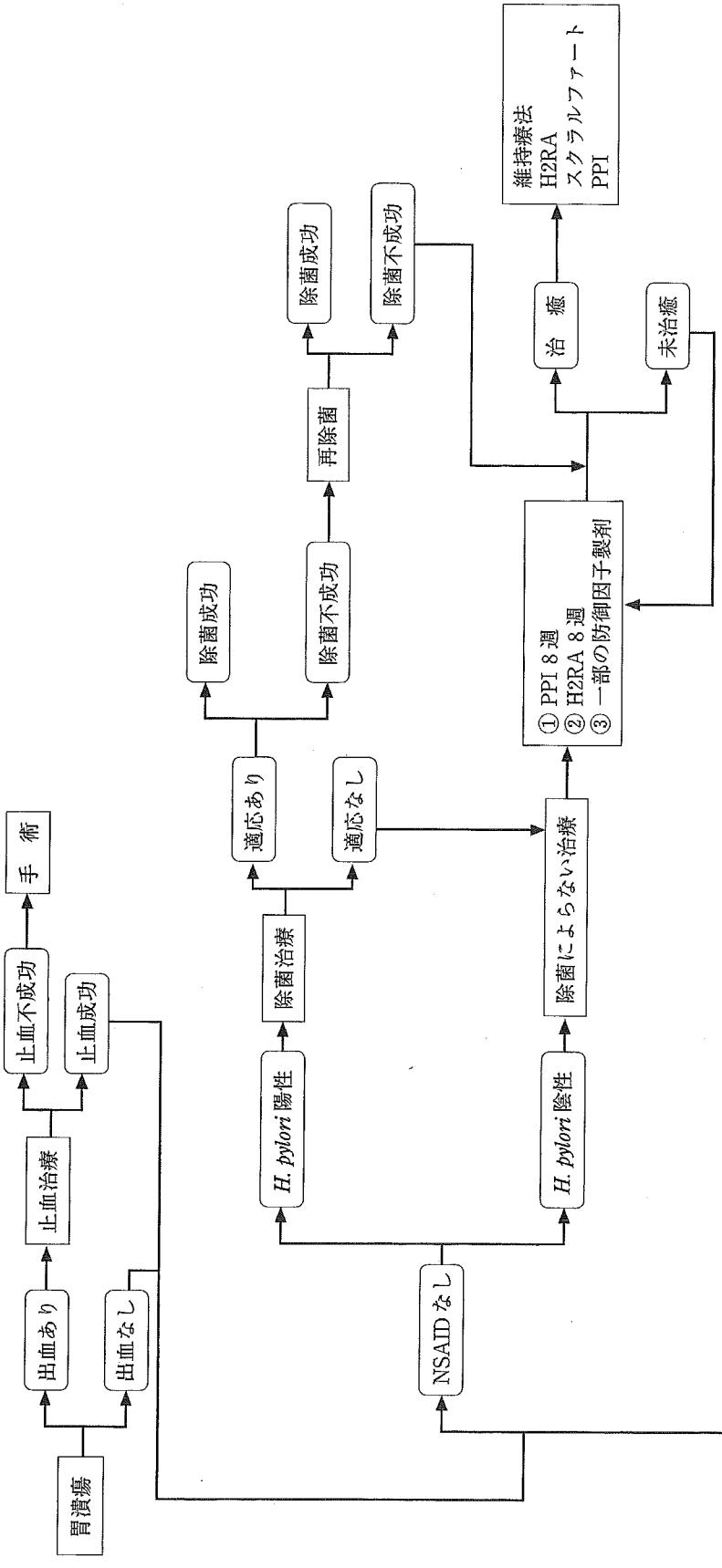

図1　胃潰瘍診療の流れを示すフローチャートの概略

法の必要性に関するエビデンスは今後の課題である．

3. 胃潰瘍診療ガイドラインの意義と問題点

EBMによる胃潰瘍診療ガイドラインはこれまでの専門家による従来の診療指針とは大きく異なる方法によって作成され，その結果従来とは異なる新たな方針を提示している．

すなわち，①成因論に応じた治療指針の明示，②潰瘍薬における治療選択の優先順位の明確化，③単剤治療の推奨，④有効性のエビデンスが明確でない治療法の排除，⑤医療経済的配慮，⑥患者向けの診療指針の公開などである．このガイドラインでは，その指針の基盤となる日本人のエビデンスが十分ではない点があることは確かであり，それらの必要性が認識された点も一つの意義であろう．また，今後はきちんとした研究計画に基づいて行われた確固としたエビデンスが必要であり，それぬきで今後の胃潰瘍診療指針の改定は論じられないという認識が専門家の間にも，薬剤メーカーの間にも浸透したことは確かであろう．いいかえれば，古いエビデンスのみに依拠している薬剤については，今後その存在意義が問われることになるであろう．

一方，ガイドラインの問題点としては，エビデンスに基づいた指針を作成する必要性から，現行の保険制度では必ずしも許容されない指針を示した部分もある．今後，エビデンスからみて最良とはいえない現行の保険診療制限については見直しを検討すべきであろう．そのためには，そのようなガイドラインと保険診療制度の齟齬にかかわる問題点を医師のみならず一般国民にインターネットを通じて公開し，国民の問題意識に基づいて保険診療制度の改革を行政に反映していけるようなフィードバックが行われることが期待される．また今回の胃潰瘍診療ガイドラインでは，ある程度日本人のデータが拾い上げられたとはいえ，まだエビデンスとして不十分な点が多いことは否めない．例えば抗潰瘍薬のNSAID潰瘍の治療や予防についての有効性を示す我が国のデータは皆無である．今後我が国の製薬企業が日本人の科学的なエビデンスを蓄積することにもっと熱意をもち，エビデンスに基づく日本人の潰瘍治療体系がより充実できるよう貢献していくことが求められる．

更に，ガイドラインを実地臨床で使用していった場合，どのような問題点があるのか，また実地臨床に適用した場合に従来の治療方針と比較してどのような効果があるのかについて検証を行う必要がある．このようなアウトカム研究も今後の改定作業を考えるうえで重要な要素となるであろう．将来，ガイドラインはそのようなアウトカム研究の結果を参考にし，また新たなエビデンスの集積，医療体制の変化に応じて改定していく必要がある．日本医療機能評価機構がガイドラインの改定を支援する構想が考えられているが，実際の作業には膨大な時間と労力が必要であり専門学会の協力なしにはガイドラインの維持，改定は困難であると思われる．胃潰瘍診療ガイドラインについても，日本消化器病学会に作業部会を設け，今後の改定や新たなガイドライン作りを行う体制を検討しているところである．

おわりに

胃潰瘍診療ガイドラインは，EBMの手法によって作成された初めての診療指針であり，従来の専門家の手になる治療指針とは異なる視点から新しい胃潰瘍診療体系を提唱することとなった．またこのガイドラインを作成することによって，今後必要となるエビデンスや，あいまいであった診療指針が明確になったことは間違いない．今後の胃潰瘍診療ガイドラインは，いずれ改定されるにせよ，少なくとも従来型の専門家個人の手になる診療指針とは決別し，明確な科学的エビデンスに依拠する形式が踏襲されると思われる．

文　献

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Comparison of hemostatic effects by route of H_2 receptor antagonist administration following endoscopic mucosal resection in patients with neoplastic gastric lesions

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SUMMARY

Background: To date, there has not been an in-depth investigation to identify differences in the effects of bleeding prevention among different routes of administration of H_2 receptor antagonists to treat gastric ulcers following endoscopic mucosal resection (EMR).
Aim: To prospectively compare the frequency of bleeding following EMR between patients treated with intravenous(IV) famotidine and those with oral famotidine.
Methods: Fifty-three patients with neoplastic gastric lesions (33 carcinoma and 20 adenoma) treated by EMR were included. Subjects underwent EMR with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate (EMRSH), followed by IV or oral (PO) administration of famotidine at a dosage of 40 mg/day for 2 days. Patients with odd ID numbers were assigned to IV therapy (30 cases) while even numbers were given PO therapy (23 cases). Frequencies and endoscopic findings of bleeding during the first 2 days after EMR were examined.
Results: Frequency of bleeding within 2 days after EMR was 3 and 4% in IV and PO patients, respectively, showing no significant difference. No significant difference was seen in the endoscopic findings of bleeding and therapy, either, with respective IV and PO findings at 23 and 26%.
Conclusions: No significant difference was observed in frequency of bleeding within 2 days after gastric EMR between IV and oral administrations of famotidine.

INTRODUCTION

Hemostasis is essential after endoscopic mucosal resection (EMR) to treat neoplastic gastric lesions. Generally, it is performed by fasting, fluid replacement by drip infusion, and intravenous (IV) administration of an H_2 receptor antagonist (H_2RA) to control acid secretion.

Few studies have been made to investigate the antibleeding effects of H_2RA administration to treat gastric ulcers following EMR with a focus on the route of administration, and no concrete evaluation has been established. Oral administration is considered more favorable in terms of both patient quality of life (QOL) and economic efficiency, on the condition that it produces an effect equivalent to that of IV route. This study was conducted to prospectively compare the frequency of bleeding between patients given post-EMR oral or IV famotidine.

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MATERIALS AND METHODS

Fifty-three patients with neoplastic gastric lesions (gross mucosal carcinoma that were categorized as

differentiated early gastric carcinoma or adenoma) underwent EMR, including 33 with carcinoma and 20 with adenoma. Subjects' histologic types included 26 tubular adenocarcinoma, five papillary adenocarcinoma, and two tubular and papillary adenocarcinoma. Patients were excluded from the study if they had (i) a previous history of upper gastrointestinal surgery or vagotomy; (ii) any serious complications including cardiac, hematologic, renal, and/or hepatic disease; (iii) a history of previous allergy to an H_2RA; (iv) ongoing medication that has interaction with H_2RA (theophylline or phenytoin); (v) a complication of gastric/duodenal ulcer excluding ones at a healed stage; (vi) ongoing warfarin therapy; and/or (vii) his/her attending physician's decision that the patient would be ineligible for inclusion in the study. Patients assigned with odd ID numbers were selected to receive famotidine intravenously (IV), whereas those with an even number were assigned to receive famotidine orally (PO).

The EMR with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate (EMRSH) was conducted[1, 2]. To elevate the mucosa, 0.5% sodium hyaluronate (SH) added with 0.001% epinephrine and 0.004% indigo carmine dye was locally injected using a 23-gauge needle. Coagulation with hemostatic forceps or hemoclipping was performed to control intra-operative bleeding, if necessary.

Patients were subject to fasting on the day of and the day after the EMR treatment. During these 2 days, IV-treated patients were given 20 mg of famotidine (Yamanouchi Pharmaceutical, Japan) diluted with 50 mL of normal saline solution twice a day, while receiving an infusion of 1500 mL of Solita T3 (Shimizu Pharmaceutical, Japan). The other patients orally took one tablet of famotidine D (20 mg) (Yamanouchi Pharmaceutical, Japan) twice a day, with a 1500 mL oral fluid replacement of Solita T3 granule (Shimizu Pharmaceutical, Japan). Concomitant use of antisecretory drugs other than famotidine, antiacids, and mucosal defensive agents was prohibited, while the use of sodium alginate and thrombin powder was allowed.

Upper gastrointestinal endoscopy was conducted 2 days after EMR to identify any bleeding from the ulcer on the resection site, using Forrest's classification.[3] Major findings of bleeding included group Ia (spurting hemorrhage), Ib (oozing hemorrhage), IIa (non-bleeding visible vessel), and IIb (adherent clot). In the case of hemorrhagic lesion, eradication therapy was given by either hemoclipping or local infusion of hypertonic saline-epinephrine (HSE). When there was no hemorrhagic episode, patients were permitted to eat from the evening of the same day. From the second day onward after EMR, patients orally took one tablet of famotidine D (20 mg) two times per day. Endoscopy was performed on the seventh day after EMR, and patients were discharged from the hospital on the eighth day if no bleeding from an ulcer was observed, while the fasting period was extended in patients with bleeding.

The first end-point of evaluation was the frequency of bleeding on the second day after EMR. Bleeding was evaluated based on any clinical evidence of bleeding, including hematemesis and tarry stool. Hemoglobin level on the first day was determined, as well as any endoscopic finding of bleeding on the second day. Other evaluations included days from EMR to the resumption of a diet and number of days in the hospital.

This study was conducted upon approval of the ethical committee of Jichi Medical School and written informed consent was obtained.

Statistic analysis was performed using the Mann–Whitney *U*-test, Fisher's exact probability test, and Wilcoxon signed-ranks test. Statistically significant differences were determined to be established when $P < 0.05$.

RESULTS

Patient characteristics for IV and PO patients are summarized in Table 1. No item had any significant difference; slightly but not significantly more coexisting hypertension was observed in IV patients.

Characteristics of the neoplastic lesions and procedures of EMR were compared between the two routes (Table 2). There was no significant difference in the ratio of carcinoma to adenoma, tumor location and size,

Table 1. Patient characteristics

Characteristics	IV patients ($n = 30$)	PO patients ($n = 23$)	*P* value
Mean age (years)*	69.6 (8.0)	66.4 (9.7)	0.44
Sex (M/F)	23/7	18/5	>0.99
Smoking	15 (50%)	9 (39%)	0.58
Drinking	16 (53%)	11 (48%)	0.78
Hemoglobin (g/dL)*	3.5 (1.2)	13.8 (1.1)	0.28
Coexisting hypertension	15 (50%)	7 (30%)	0.06

*Values are mean (s.d.).

Table 2. Characteristics of the neoplastic lesions removed by procedure of EMR

Details	IV patients (n = 30)	PO patients (n = 23)	P value
Cancer/adenoma	20/10	13/10	0.57
Tumor location (L/M/U)	6/16/8	9/12/2	0.14
Tumor size (mm)*	22.3 (11.5)	18.3 (11.3)	0.12
Size of resected area (mm)*	39.2 (14.3)	34.1 (11.4)	0.20
Amount of SH injected (mL)*	39.0 (26.0)	26.5 (12.9)	0.08
Time of EMR (minutes)*	89.2 (55.3)	59.0 (32.1)	0.04
Number of hemoclips used†	1 (0, 1.5)	0 (0, 1.5)	0.22

SH, sodium hyaluronate; L, lower; M, middle; U, upper third of the stomach.
*Values are mean (s.d.).
†Values are median (first and third quartile).

Table 3. Bleeding during 2 days after EMR, the endoscopic findings of bleeding, and therapy on the second day after EMR

	IV patients (n = 30)	PO patients (n = 23)	P value
Tarry stool	1 (3%)	1 (4%)	>0.99
Endoscopic findings of bleeding	7 (23%)	6 (26%)	>0.99
Ia	1	1	–
Ib	2	2	–
IIa	4	2	–
IIb	0	1	–
Hemostatic therapy	6 (20%)	6 (26%)	0.74

size of resected area, amount of SH injected, and number of hemoclips used. Time of EMR was longer in IV patients. In both treatment segments, en-bloc resection was achieved in all patients by EMR.

Bleeding during 2 days from EMR was 3 and 4% for IV and PO patients, respectively, representing no significant difference (Table 3). A 66-year-old woman treated with IV famotidine had gastric carcinoma measuring 21 mm in diameter in gastric antrum (Figure 1), but use of hemoclip was not necessary at the time of EMR (Figure 2). She had a small amount of tarry stool on the second day after EMR, and on the same day endoscopy revealed oozing on the ulcer base and one visible vessel (Figure 3), in both of which one and two hemoclips were placed, respectively (Figure 4). No bleeding was observed thereafter, and 7 days after EMR the ulcer base appeared as a clean whitish exudate. A 74-year-old man treated with oral famotidine had gastric carcinoma measuring 35 mm in diameter in the gastric antrum,

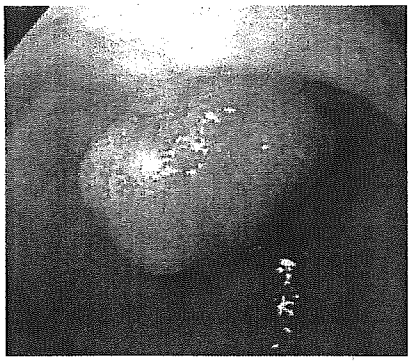

Figure 1. An IV-treated 66-year-old woman with a 21 mm stomach cancer in the lesser curvature of the gastric antrum.

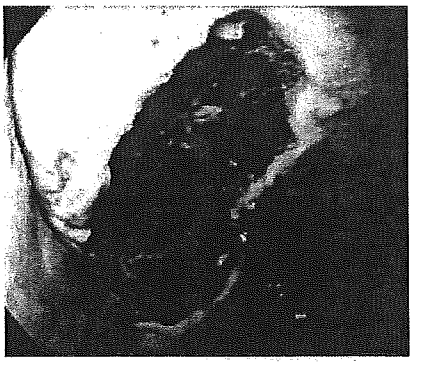

Figure 2. After the completion of EMR, the size of resected area measured 32 mm, no hemoclipping was necessary during EMR.

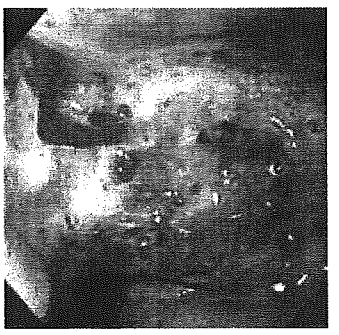

Figure 3. Endoscopic evaluation on the second day after EMR, one oozing and one visible vessel were observed on the ulcer base.

and hemoclipping was not necessary at the time of EMR. There was one observation of tarry stool on the first day after EMR, and the following day visible vessels were observed in three sites by endoscopy. A local

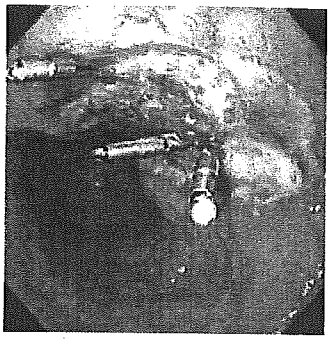

Figure 4. A hemoclip was placed on the site of oozing, and two on the visible vessel.

infusion of 1.5 mL HSE and one hemoclipping were performed on each site. Endoscopy on the seventh day from EMR found the ulcer base appeared as a clean whitish exudate.

Hemoglobin levels on the first day after EMR did not decrease from those prior to the therapy in both patients [IV: 13.4 ± 1.1 (mean ± s.d.) g/dL vs. 13.5 ± 1.1 g/dL before and 1 day after the therapy, respectively, PO: 13.9 ± 1.2 g/dL vs. 14.1 ± 1.2 g/dL, respectively). No case experienced hemorrhagic shock or required transfusion following EMR. There was a case in which urgent endoscopy was performed due to bleeding after the second day from EMR; a 66-year-old female patient treated IV had a 33 mm adenoma in the body and had two hemoclips placed during the EMR. There was no finding of hematemesis or melena following EMR, and endoscopy on the second day after EMR found no bleeding. She experienced hematemesis of approximately 300 mL in the morning of the seventh day after EMR, but there was no decrease in blood pressure or tachycardia found. Endoscopy revealed an oozing on the ulcer base, thus two hemoclips were placed and a local infusion of 2.5 mL of HSE was given to stop bleeding. The patient was then given a proton pump inhibitor (PPI) and later discharged once no bleeding was found by endoscopy on the seventh day after the endoscopic hemostatic therapy.

Endoscopy on the second day after EMR found bleeding in 23% of IV patients and 26% of PO patients, with no significant difference between the two (Table 3). Table 4 shows profiles of these 13 cases. Hemoclips were used to stop bleeding in all 13 subjects of both treatments but one IIa of the seven IV patients.

Period of fasting following EMR was 2.9 ± 1.2 (mean ± s.d.) days in IV patients and 2.9 ± 1.8 days in PO patients, showing no significant difference. No significant difference was seen in the length of stay in hospital, either, with 11.1 ± 1.9 days and 11.9 ± 2.9 days in IV and PO patients, respectively.

The costs (in 2004 Japanese Yen) of famotidine 20 mg injection and famotidine D 20 mg tablet were ¥387 and ¥68, respectively. The cost of 2 day famotidine IV therapy (¥1548) was more expensive than that of PO therapy (¥272). The difference was ¥1276 (approximately $12.27 calculated in US $). The costs of 1500 mL of Solita T3 and the procedure of drip infusion were ¥660 and ¥950, respectively. The cost of 15 packs of Solita T3 granule (dissolved in 1500 mL of water) was ¥367.5. The cost of 2 day drip infusion (¥3220) was more expensive than that of oral fluid replacement

Table 4. Patients profile with endoscopic findings of bleeding

No	Treatment	Age (years)	Sex	Forrest's classification	Tumor	Region	Tumor size (mm)
1	IV	70	m	Ia	Cancer	L	25
2	IV	66	f	Ib	Cancer	L	21
3	IV	74	m	Ib	Cancer	U	18
4	IV	74	f	IIa	Cancer	L	24
5	IV	52	m	IIa	Cancer	M	20
6	IV	75	m	IIa	Cancer	M	18
7	IV	78	m	IIa	Adenoma	M	27
8	PO	58	f	Ia	Cancer	L	25
9	PO	71	m	Ib	Cancer	M	20
10	PO	51	m	Ib	Adenoma	M	9
11	PO	74	m	IIa	Cancer	L	35
12	PO	74	m	IIa	Cancer	L	13
13	PO	48	m	IIb	Adenoma	M	12

L, lower; M, middle; U, upper third of the stomach.

(¥735). The difference was ¥2485 (approximately $23.89 calculated in US $).

When comparing the 13 patients with bleeding in endoscopic findings and the other 40 patients, there was no significant difference in patient characteristics (age, sex, smoking, drinking and coexisting hypertension), or in tumor characteristics [pathology (carcinoma/adenoma), location, and size], procedure of EMR (size of resected area, amount of SH administered, and number of hemoclips used).

DISCUSSION

It is a common practice to administer antisecretory drugs after EMR for neoplastic gastric lesions to prevent bleeding. Acid secretion is not high in cases of differentiated early gastric carcinoma or adenoma, as the gastric mucosa presents significant atrophic gastritis. Therefore, H_2RAs are considered to have sufficient efficacy to suppress acid secretion in such cases. Effects of H_2RA in preventing hemorrhage, however, have not been evaluated in depth in terms of difference among administration routes to treat post-EMR gastric ulcers.

Although bleeding during EMR is usually treated with procedures such as coagulation and hemoclipping and poses no clinical problem, post-operative or delayed bleeding, on the other hand, has been reported otherwise.[4] EMR forms gastric ulcer going into the submucosa, which could have damaged small vessels, and even if they have coagulated by the end of EMR, subsequent recurrence of bleeding is possible. In order to prevent bleeding, it is necessary to elevate gastric pH and improve clotting ability.[5]

Some reports claim superior benefits of PPIs over H_2RA for the prevention of recurring hemorrhage due to bleeding ulcer,[6, 7] while others report no difference.[8, 9] Given that post-EMR gastric ulcer stops bleeding by the end of treatment and that acid secretion is low in cases of significant atrophic gastritis, H_2RA is considered sufficient enough for the prevention of bleeding following EMR. In this study using famotidine, delayed bleeding was seen in only 5.7% of the cases (3/53).

Frequencies of bleeding in gastric EMR have been reported in 6.8% (5/73) by Takeshita *et al.*,[10] and 22% (9/41) by Ohkuwa *et al.* in their studies with EMR using an insulated-tip diathermic knife (IT-EMR),[11] while our study with EMRSH found the rate to be 4% (3/70).[1] Yamamoto *et al.* reasoned that the low frequencies of post-EMR bleeding is due to the use of SH, as it secures a safe mucosal incision, and maintenance of sufficient mucosal elevation poses less damage on deep tissues.[1]

Regarding the frequency of delayed bleeding following EMR in the stomach or upper gastrointestinal tract, Okano *et al.*[4] found it in 5.3% (25/476) of the subjects, and Rösch *et al.*[12] in 5.4% (2/37). The present study had similar results at 5.7% (3/53). Okano *et al.*[4] reported that the only factor significantly related to the occurrence of delayed bleeding was immediate bleeding during EMR. In the present study, one of three cases of delayed bleeding had a hemoclip placed during EMR, while the other two did not. No factor was recognized to present significant difference between cases with and without endoscopic findings of bleeding, indicating a potential difficulty in predicting the occurrence of delayed bleeding.

In the present study, no significant difference was observed between famotidine IV and PO in terms of the respective results of endoscopy or frequency of bleeding on the second day after EMR. The endoscopy performed on the second day did not show any significant difference in frequency for bleeding to be found or for hemostatic procedure to be required, nor was such difference found in the length of post-EMR fasting or hospitalization. As to the administration of H_2RA to prevent bleeding in the stomach following EMR, the oral route was shown to have sufficient effect. This result is considered preferable from the perspective of both less complicated procedure and higher cost efficiency. The cost of 2-day famotidine IV therapy (¥1548) was more expensive than that of PO therapy (¥272). The cost of 2-day drip infusion of Solita T3 (¥3220) was more expensive than that of oral fluid replacement of Solita T3 granule (¥735). Moreover, oral fluid replacement might improve patient QOL.

In conclusion, there was no significant difference demonstrated in the frequency of bleeding up to 2 days from the completion of gastric EMR between IV and oral administration of famotidine.

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Impaired Production of Gastric Ghrelin in Chronic Gastritis Associated with *Helicobacter pylori*

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Ghrelin is primarily secreted from the stomach and has been implicated in the coordination of eating behavior and weight regulation. The effects of *Helicobacter pylori* infection on plasma ghrelin concentration and gastric ghrelin production still have not been well known. We determined plasma ghrelin concentration in a total of 160 consecutive individuals with normal body mass index including 110 *H. pylori*-infected and 50 *H. pylori*-negative subjects. The expression levels of ghrelin mRNA and ghrelin-producing cells in the gastric mucosa were quantified with real-time quantitative RT-PCR and immunohistochemistry, respectively. The severity of gastric atrophy was evaluated by serum pepsinogen concentrations. Plasma ghrelin concentration, gastric ghrelin mRNA, and ghrelin-positive cell numbers in gastric mucosa were significantly lower in *H. pylori*-infected subjects. The decrease in plasma ghrelin concentration in *H. pylori*-positive subjects was accompanied by an attenuation of ghrelin mRNA expression and a reduction of ghrelin-positive cell numbers in the gastric mucosa. Moreover, lower serum pepsinogen I concentrations and I/II ratio were significantly associated with lower plasma ghrelin concentrations in *H. pylori*-positive subjects. These findings suggest that impaired gastric ghrelin production in association with atrophic gastritis induced by *H. pylori* infection accounts for the decrease in plasma ghrelin concentration. (*J Clin Endocrinol Metab* 90: 10–16, 2005)

GHRELIN, A 28-AMINO acid peptide isolated from rat and human stomach possesses strong GH-releasing activity and plays central as well as peripheral roles in food intake, gastric motility, and acid secretion (1, 2). Ghrelin has been shown to evoke weight gain by actions in the hypothalamus (3). Plasma ghrelin concentrations rise before meals and fall after meals. This peptide also contributes to the regulation of both somatic growth and adipose tissue mass and is therefore a short-term, meal-related orexigen as well as a long-term regulator of body weight (4–6). Circulating ghrelin concentrations in newborns are not associated with gender, body weight, or hormonal parameter (7). In children and adults, however, plasma ghrelin concentrations are lower in obese subjects, compared with those with normal body weight and lean subjects (8, 9). The decrease of plasma ghrelin concentrations appears to compensate for the positive energy balance in obese individuals (9). The majority of circulating ghrelin is produced in the mammalian gastric mucosa by enteroendocrine cells/oxyntic glands, probably the X/A-like cells (10). Thus, there exists the possibility that chronic persistent damage of the gastric mucosa, such as chronic gastritis, might affect ghrelin production, leading to changes in food intake and body weight. *Helicobacter pylori* is a Gram-negative bacterium that colonizes the stomach. *H. pylori* infection is involved in the pathogenesis of gastritis, gastric and duodenal ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma (11–13). More than 50% of the adult population are infected with *H. pylori* worldwide (14, 15). *H. pylori* infection first leads to atrophic gastritis and intestinal metaplasia, which may further lead to dysplasia and gastric carcinoma (16). Thus, it is an intriguing question whether *H. pylori* infection affects gastric ghrelin production and consequently alters plasma ghrelin concentration.

In this respect, Nwokolo *et al.* (17) reported that plasma ghrelin concentrations increased after the eradication of *H. pylori*. On the contrary, Gokcel *et al.* (18) reported that *H. pylori* infection has no effect on plasma ghrelin levels. Thus, the relationship between *H. pylori* infection and plasma ghrelin concentrations is still controversial, prompting us to further assess the effects of *H. pylori* infection on plasma ghrelin concentrations. Because previous studies examined serum ghrelin concentrations without investigating gastric ghrelin production (17, 18), the direct relationship between *H. pylori* infection and gastric ghrelin production, which could influence plasma ghrelin concentrations, is still to be demonstrated. We thus conducted this study to investigate the association of *H. pylori* infection with both ghrelin mRNA and protein production in the stomach, concomitantly examining plasma ghrelin concentrations. To this end, we applied real-time quantitative RT-PCR and immunohistochemistry of endoscopic biopsy specimens. Moreover, because body weight is an important factor that determines plasma ghrelin concentrations, only individuals with normal body mass index (BMI) were enrolled in this study. We report here that *H. pylori* infection is associated with lower gastric ghrelin mRNA and protein as well as serum ghrelin concentrations.

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Abbreviations: BMI, Body mass index; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

Subjects and Methods

Participants

We enrolled 160 consecutive asymptomatic men with normal BMI undergoing gastric cancer surveillance in Tochigi, Japan. They were divided into two groups (110 *H. pylori*-positive subjects and 50 *H. pylori*-negative controls) according to the presence or absence of *H. pylori* in the gastric mucosa evaluated by the bacterial culture and histological examination. The percentage of the *H. pylori*-positive subjects was similar to that of the same generation in Japan. *H. pylori*-positive subjects included 23 patients with chronic gastritis alone, 50 patients with chronic gastritis and gastric ulcer, 27 patients with chronic gastritis and duodenal ulcer, eight patients with chronic gastritis and gastric polyp, and two patients with chronic gastritis and gastric adenoma. Neither atrophic changes nor any other abnormal findings were observed in the 50 controls without *H. pylori* infection by endoscopic or histological examination. Their characteristics were similar to those of the *H. pylori*-positive subjects in age, gender, BMI, serum cholesterol, and fasting blood sugar as shown in Table 1. No subjects had evidence of a cachectic state such as advanced cancer, thyroid disease, liver disease, or infection. Subjects with diabetes mellitus or renal dysfunction (serum creatinine ≥1.5 mg/dl) were excluded. None of the 160 individuals recruited had a history of eradication therapy for *H. pylori* infection or received any antibiotic treatment during the study. Written informed consents were obtained from all participants in accordance with the Declaration of Helsinki and its later revision. This study was approved by the Ethics Committee of the Jichi Medical School. Subjects with *H. pylori* infection were classified into three groups according to the fasting levels of plasma ghrelin as shown in Table 2: low ghrelin group (<70 fmol/ml; n = 34), middle ghrelin group (70–150 fmol/ml; n = 36), and high ghrelin group (>150 fmol/ml; n = 40). Age, BMI, serum lipid data, and fasting blood sugar were similar in those three groups.

Specimens

Five adjacent biopsy specimens from the greater curvatures at the midcorpus of the stomach as well as five from the antrum were obtained endoscopically from all subjects. One biopsy specimen from the corpus of the stomach and one from the antrum were cultured individually to evaluate for the presence of *H. pylori* infection. Three biopsy specimens from the corpus and three from the antrum were immediately snap frozen and stored in liquid nitrogen for later use. The remaining corpus and antral specimens were fixed and stained with hematoxylin and eosin, Giemsa, and antighrelin antibody. Histological assessments were performed by a single observer (H.Os.). *H. pylori* infection was evaluated by the bacterial culture and histological examination.

Hormone assays

Blood was drawn into chilled tubes containing EDTA-2Na (1 mg/ml) and aprotinin (500 U/ml), and plasma was harvested after immediate centrifugation and stored at −30 C until assay. Plasma ghrelin levels were measured by a RIA developed in our laboratory. In brief, antiserum against the C-terminal region of human ghrelin was raised in New Zealand white rabbits that were immunized against synthetic human ghrelin (13–28). Human Tyr^0-ghrelin (position13–28) was radioiodinated by the lactoperoxidase method for use in the assay. Inter- and intraassay variation was less than 8 and 6%, respectively. The limit of detection of this assay is 12 fmol per tuve of human ghrelin. We described previously the properties of the antiserum for ghrelin used in this study (9, 10).

TABLE 1. Characteristics of *H. pylori*-negative and -positive subjects

	H. pylori-negative (n = 50)	*H. pylori*-positive (n = 110)	*P*
Age (yr)	47.4 ± 1.1	48.8 ± 0.6	0.58
BMI (kg/m^2)	22.5 ± 0.4	21.9 ± 0.2	0.21
T-Chol (mg/dl)	196 ± 4	194 ± 3	0.71
HDL-C (mg/dl)	61.4 ± 2.7	60.7 ± 1.2	0.79
Triglyceride (mg/dl)	99 ± 6	93 ± 4	0.34
FBS (mg/dl)	96 ± 2	94 ± 1	0.18

Data are the mean (± SE). T-Chol, Total cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar.

TABLE 2. Characteristics of low, middle, and high ghrelin groups in *H. pylori*-positive subjects

	Low (n = 34)	Middle (n = 36)	High (n = 40)
Age (yr)	50.1 ± 1.1	48.3 ± 0.9	48.0 ± 1.1
BMI (kg/m^2)	21.9 ± 0.3	21.9 ± 0.3	21.8 ± 0.2
T-Chol (mg/dl)	196 ± 6	186 ± 5	198 ± 5
HDL-C (mg/dl)	59.8 ± 2.6	61.1 ± 2.1	61.1 ± 1.8
Triglyceride (mg/dl)	96 ± 7	88 ± 7	94 ± 7
FBS (mg/dl)	95 ± 2	93 ± 1	93 ± 2

Data are the mean (± SE). T-Chol, Total cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar.

Immunohistochemistry

We generated antighrelin antiserum as described previously (10). Briefly, synthetic [Cys^{12}]rat-ghrelin (position 13–28) (4 mg) was conjugated with maleimide-activated mariculture keyhole limpet hemocyanin (6 mg; Pierce Chemical Co., Rockford, IL). The antigenic conjugate solution was administered to a New Zealand White rabbit. The antirat ghrelin antiserum (G107) specifically recognizes ghrelin and has 100% cross-reactivity with human ghrelin in immunohistochemistry (10).

Paraffin-embedded sections of the biopsy samples taken from the greater curvature of the stomach were deparaffinized in xylene, immersed in citrate buffer [10 mM (pH 6.0)], heated at 120 C for 20 min in an autoclave, and left at room temperature for 60 min. After incubation with blocking reagent (Dako Japan, Kyoto, Japan) for 10 min, individual sections were incubated with antiserum for ghrelin (diluted to 1:500) in a moist chamber at 4 C overnight. Normal mouse IgG_1 was used for control studies. The slides were then washed five times with PBS and incubated with dextran polymer system/peroxidase (EnVision+; Dako Japan) at 37 C for 60 min. The chromogen was developed by incubating the slides with diaminobenzidine solution for 3 min. The slides were counterstained with hematoxylin.

RNA extraction

Total RNA was isolated from the biopsy specimen with ISOGEN (Nippon Gene, Tokyo, Japan). Two microgram of total RNA from each sample was reverse transcribed by using random nanomers and reverse transcriptase (TOYOBO, Osaka, Japan) according to the manufacturer's protocol.

Real-time quantitative RT-PCR

The expression level of ghrelin mRNA was evaluated by using a real-time quantitative RT-PCR method with an ABI 7700 sequence detector system (PE Applied Biosystems, Foster City, CA). The sense primer for ghrelin was 5′-GGCAGGCTCCAGCTTCCT-3′ and the antisense primer was 5′-TGGCTTCTTCGACTCCTTTCTC-3′. The reaction mixture was prepared according to the manufacturer's protocol using TaqMan PCR kits (PE Applied Biosystems). The reactions also contained target hybridization ghrelin probe labeled with a reporter fluorescent dye, 6-carboxyfluorescein, at the 5′ end (5′-AGCCCTGAACACCAGAGA-3′). The thermal cycling conditions included 50 C for 2 min and 95 C for 10 min, followed by 15 sec of denature at 95 C and 1 min of annealing/extension at 60 C for 40 cycles.

The quantitative amplification and expected sigmoid curve of PCR were obtained. The PCR products were also examined by 2% agarose gel electrophoresis to confirm successful amplification of the expected size of the gene. As a control, the mRNA was also subjected to real-time quantitative RT-PCR for measurement of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) using TaqMan GAPDH control reagents (PE Applied Biosystems). For relative quantification of the ghrelin expression, calibration curves were constructed using the mRNA obtained from normal gastric mucosa without *H. pylori* infection. mRNA for GAPDH was used as an endogenous control. The levels of ghrelin mRNA were calculated from the ratio of ghrelin mRNA level to GAPDH