厚生労働科学研究費補助金
第３次対がん総合戦略研究事業

ピロリ感染率減少時代における新しい対策型胃がん検診システム構築の検証に必要なプロトコール作成と実現可能性に関する研究

平成２２年度　総括研究報告書

研究代表者　後藤田　卓志

平成２２（２０１１）年　５月

目　　次

厚生労働科学研究費補助金（第３次対がん総合戦略研究事業）
総括研究報告書

ピロリ感染率減少時代における新しい対策型胃がん検診システム構築の検証に必要なプロトコール作成と実現可能性に関する研究

研究代表者　後藤田　卓志　（国立国際医療研究センター病院　医長）

研究要旨

本研究「ピロリ感染率減少時代における新しい対策型胃がん検診システム構築の検証に必要なプロトコール作成と実現可能性に関する研究」（GAstric cancer screening LAbeled by serum examination in Place of Aged Gastric cancer Organized Screening System -GALAPAGOSS Study-）は、対策型胃がん検診で用いられている「X線検査（バリウム検診）」群と、「ピロリ菌抗体+ペプシノゲン測定（血清胃がんリスク検診）」群に無作為に振り分け比較することで、ピロリ菌感染率減少時代における新しい対策型胃がん検診システムの検証を目的としている。平成22年度より3年計画で本研究を開始し、初年度では文献調査、医師・研究者・検診機関ヒアリングなど重ね、研究プロトコールを完成させた。平成23年度はプロトコールに従って、秋田県由利本荘市やＪＡ秋田の協力を得て研究計画に沿って毎年500例の症例集積を目標に6年間の前向き比較試験がスタートする。

研究者名	所属施設および職名
後藤田卓志	国立国際医療研究センター病院消化器内科　医長
菅野健太郎	自治医科大学消化器内科　教授
大西洋英	秋田大学大学院医学系研究科・消化器内科学　教授
松山　裕	東京大学大学院医学系研究科・生物統計学　准教授
福田　敬	東京大学大学院医学系研究科　臨床疫学・経済学分野　准教授
稲葉　一人	中京大学法科大学院　教授
小西　宏	日本対がん協会・がん検診研究室　研究員

A．研究目的

本研究の目的はピロリ感染率減少時代における新しい対策型胃がん検診システムを構築するために、実現可能な比較試験のプロトコールを完成し前向き研究を遂行することである。

対策型胃がん検診は、「40歳以上を対象に年に１回、X線検査」（国の指針）を行い、胃がんの疑いがあると判断された場合（要精密検査）に、内視鏡等で詳しい検査(生検を含む)を行っている。胃がんの死亡率減少に寄与したことが症例対照研究やコホート研究などで証明され、指針では推奨グレードBとしている。しかし、科学的な証拠能力が高い無作為化比較試験は実施されていない。

平成19年度の対策型胃がん検診の受診者は426万人で（対象は40歳以上の男女で約6,000万人)、胃がんは約6,500人に発見された。１人あたりの検診費用を考慮すると200億円以上かけて6,500人の胃がん（約300万円/胃がん）を発見している。一方、新たに胃がんと診断される人は年に10万人と推定されている。この乖離は胃がんが、がんの罹患者トップを占めた時代では許容された社会的コストである。

胃がん発生はピロリ菌感染との関連が強く示唆されている。一方で、ピロリ菌感染率が低い（20%～30%）45歳以下の世代が「胃がんの好発年齢（65歳)」に入る時代には、胃がんの発生率の減少も確実視される。このような中、現在の対策型検診が効果的・効率的なのかどうか、費用対効果の面からも疑問がある。さらに、対策型胃がん検診の受診率も年々減少し（平成20年度地域保健・健康増進事業報告によると、平成20年度は10.2%)、「がんによる死亡率の20%減」を目指すがん対策推進基本計画が目標に掲げる「50%以上」の達成は困難である。

近年、萎縮性胃炎のある人は、胃がん高危険群に属するとの考えから、萎縮性胃炎との相関がある血清ペプシノゲン値（PG）を測定し、胃がんの高危険群を明らかにしようという方法が考案された。さらに、ピロリ抗体（HP）を同時に測定し、危険度に応じて受診者をＡ群(HP陰性かつPG陰性)、Ｂ群（HP陽性かつPG陰性)、Ｃ群（PG陽性）に分けるＡＢＣ検診（理論）が提唱された。この方法を用いて、一部自治体や企業の検診でPGとHP抗体を同時に測定することによる高危険群の抽出が行われている。

科学技術の進歩による新しい検査方法に対する、「有効性評価に直結した研究が喫緊の課題である」（「有効性評価に基づく胃がん検診ガイドライン」）り、本研究の最終ゴールも既存の方法と新規方法の大規模比較研究である。しかし、初めから大規模な研究を計画しても机上の空論で終わることがある。よって今回の研究は、小人数を対象に、「計画総括的」「計画実効的」「統計的」「法倫理的」「医療経済的」な観点から検討を加え、エビデンスのための前向き比較研究のプロトコールを完成し、実行可能性を検証した後に、実際の臨床研究を遂行することを目的としている。

B．研究方法

１．目的

現在の一般に広く普及している対策型胃がん検診で用いられている手法である「X線検査・精査内視鏡検査群」（バリウム検診群）と、「ピロリ菌抗体+ペプシノゲン測定・内視鏡検査群」（胃がんリスク検診群）に無作為に振り分け比較することで、新しい胃がん検診システムの評価を行う。

２．対象者条件

（１） 対象条件

(ア)秋田県の本荘由利地域における対策型胃がん検診受診者（30歳以上、74歳以下)。

(イ)通常の胃がん住民検診の申し込み者を対象にし、申込み時に本研究について説明し、同意を得られた者。

（２） 除外基準

(ア) 胃がんの既往歴のある者（上皮内がんを含む)。

(イ) 過去５年以内に胃がん以外の悪性腫瘍の既往のある者（同)。

(ウ) 胃や十二指腸の切除既往者

(エ) ５年以上の生存が期待できない重篤な全身疾患を有する者。

(オ) 同意が困難な者。

(カ) その他、医師が不適切と認めた者。

（３） 参加者に対する中止基準

次の状況において、担当医師は参加者に対する研究を中止する。ただし、いかなる事態においても、参加者の安全を最優先する。

(ア) 重篤な有害事象が発現し、研究の参加継続が安全性に著しく影響を及ぼす場合。

(イ) 参加者から同意の撤回があった場合。

(ウ) 患者の適格性に問題があったことが、登録後判明した場合。

(エ) その他、担当医師が投与を中止すべきと判断した場合。

３．説明と同意（インフォームド・コンセント）

（１） 説明

研究担当者が、個別に面談により対象者本人へ下記の内容を詳しく説明する。説明・同意文書は、説明するときに対象者本人に手渡す。

(ア) この研究の目的。
(イ) どちらの群になるかは、無作為（ランダムに決める方法）で決められること。
(ウ) この臨床試験への参加は自由で、参加しなくても不利益を受けないこと。
(エ) この臨床試験への参加に同意した場合でも随時これを撤回できること。
(オ) より有効な治療法が判明した場合について。
(カ) 個人情報はエントリー施設で保管、管理され厳重に保管され、プライバシーや医療記録は守秘される。試験データは個人情報（生年月日、性別を除く）を削除して匿名化され、大阪市内に設置された京都府立医科大学大阪研究室内の事務局で管理される。

（2） 同意の取得

説明を行い、対象者がこれらの研究の内容をよく理解したことを確認した上で、研究への参加を依頼する。対象者が研究参加に同意した場合は、説明文書に自署による署名を得る。

（3） 同意取得時期

同意の取得は登録の前とする。

（4） 同意書の保管・管理

同意書は説明文書と一体型で 2 部作成し、一部は事務局に保管し、一部は被験者に交付する。

4．研究方法

(1) 研究の手順

(ア) 研究担当者は、対策型胃がん検診受診者に対して「登録適格性確認票」のチェックリストを用いて、適格か否かを判断する。
(イ) 適格条件を満たした場合、対象者に本試験の存在を説明し、参加同意を得る。
(ウ) データセンターにインターネットでアクセスして、最小化法により（層別化因子：性別と年齢；30-59 歳と 60-74 歳）割り付けを行い、X 線検査・精査内視鏡検査群（バリウム検診群）またはピロリ菌抗体+ペプシノゲン測定・内視鏡検査群（胃がんリスク検診群）の２群に分け、それぞれの検査を行う。
(エ) 研究の適格性確認票に必要事項を記入して（個人情報匿名化登録番号での運用）、データセンターにＦＡＸする。
(オ) X 線検査・精査内視鏡検査群（バリウム検診群）では毎年または隔年の検診（少なくとも観察期間 6 年間で 3 回）、ピロリ菌抗体+ペプシノゲン測定・内視鏡検査群（胃がんリスク検診群）では亜群に従った内視鏡検査結果をケースシートに記入してデータセンターにＦＡＸする。
(カ) 観察最終6年目の両群の内視鏡検査結果を同様にケースシートに記入してデータセンターにＦＡＸする。
(キ) 研究参加者への検査結果の通知は、JA 秋田厚生連由利組合総合病院保健福祉活動室より行う（参考資料）。
(ク) 経過観察の検診時に上記検診スケジュール以外で上部消化管内視鏡または上部消化管二重造影レントゲン検査を行ったか否かを把握しデータセンターに報告する。

(2) 登録場所

登録は JA 秋田厚生連由利組合総合病院保健福祉活動室にて行う。登録情報は JA 秋田厚生連由利組合総合病院保健福祉活動室およびデータセンターで管理する。

(3) 割り付け方法

割付方法は、性別と年齢（30-59 歳と 60-74 歳）を割付因子とした最小化法を用いて、無作為に「X 線検査・精査内視鏡検査群」（バリウム検診群）と「ピロリ菌抗体+ペプシノゲン測定・内視鏡検査群」（胃がんリスク検診群）に分ける。

(4) 有害事象

有害事象が発生した場合、その都度、研究責任者（班長）または班長協力者は「有害事象報告書」に必要事項を記入し、データセンターに FAX する。

5．検査および評価項目

（1） X 線検査・精査内視鏡検査群」（バリウム検診群）

(ア) 研究参加同意後に「X 線検査・精査内視鏡検査群」（バリウム検診群）に割り付けられた場合、胃 X 線検査を行う。
(イ) 所見の読影は、日本消化器がん検診学会の「新・胃Ｘ線撮影法ガイドライン」に沿って、秋田県由利本荘市の通常のダブルチェック評価方法で行う。
(ウ) X 線検査読影結果にて要精査となった場合はその理由を記録し、秋田県由利本荘市の通常の二次検診手続きに従って上部消化管内視鏡検査受診を勧告する。なお、上部消化管内視鏡検査および必要と判断した場合の生検検査は保険診療として二次検診提供施設にて実施する。

(エ) 二次検診結果は、JA秋田厚生連由利組合総合病院保健福祉活動室を通して追跡調査する。なお、胃がん（上皮内がんを含む）を認めた場合は、その部位、大きさ、進行度、組織型など胃癌取扱い規約第14版に従って記載表記する。

(オ) 2年目以降のX線検査は逐年受診を原則とするが、研究観察期間内に最低3回のX線検査を受診することとする。検診期間は、少なくとも2年以上開けないこととする。

（2） ピロリ菌抗体+ペプシノゲン測定・内視鏡検査群（胃がんリスク検診群）

(ア) 研究参加同意後にピロリ菌抗体+ペプシノゲン測定・内視鏡検査群（胃がんリスク検診群）に割り付けられた場合、採血を行った後にJA秋田厚生連由利組合総合病院にて上部消化管内視鏡検査を行う。

(イ) 上部消化管内視鏡検査にて異常を認めた場合は生検検査を保険診療として実施する。なお、胃がん（上皮内がんを含む）を認めた場合は、その部位、大きさ、進行度、組織型など胃癌取扱い規約第14版に従って記載表記する。

(ウ) 2年目以降の胃がん検診は、A群（ピロリ菌－、PG－）は研究終了時の6年目のみ、B群（ピロリ菌＋、PG－）は3年おき、C群（ピロリ菌＋、PG＋）は2年おき、D群（ピロリ菌－、PG＋）は逐年（研究観察期間内に最低3回の受診）、のスケジュールで実施する。

(エ) ピロリ菌除菌既往のある者は、除菌成功・不成功に関わらず、ピロリ菌抗体価に関わらず、ピロリ菌感染陽性としてA～D群に割り付ける。

（3） 研究最終年（6年目）の上部消化管内視鏡検査

(ア) 研究参加者全員に対して、JA秋田厚生連由利組合総合病院にて上部消化管内視鏡を実施する。

(イ) 上部消化管内視鏡検査にて異常を認めた場合は生検検査を保険診療として実施する。なお、胃がん（上皮内がんを含む）を認めた場合は、その部位、大きさ、進行度、組織型など胃癌取扱い規約第14版に従って記載表記する。

(ウ) その後、状況の許す限り長期間にわたり、本試験の参加者は追跡調査を実施する。

（4） 血液検査

(ア) 研究参加同意後にX線検査・精査内視鏡検査群（バリウム検診群）に割付られた場合でも、ピロリ菌抗体+ペプシノゲン測定を行い登録する。

(イ) 由利本荘市のがん検診にて通常実施されている血液検査項目（末梢血球数、肝機能、脂質、血糖など）を登録する。

(ウ) なお、血清サンプルは凍結保存するが、遺伝子検索には用いない。

（5） 食事調査、生活習慣アンケートなど

(ア) 研究参加時に自記式食事摂取頻度票（FFQ）にて食事内容を把握し記録する。

(イ) 生活習慣に関するアンケートは、由利本荘市のがん検診にて通常実施されている健康調査票を用いて把握し記録する。

(ウ) ピロリ菌除菌の有無と結果は、研究参加時および毎回の検査時に確認して登録を行う。

（6） 胃がん検診費用計算

(ア) 本研究のプロトコールにて必要とした全ての検査費用を登録する、

(イ) 計画以外の任意の全ての胃がん検診の有無と検査項目、費用を把握し登録する。

6．エンドポイント、予定症例数とその算定根拠、症例集積期間

（1） エンドポイント

主エンドポイントは、研究期間内の検査費用総額から検査1例あたりの平均値の比較を各群で比較すること。また、各群において胃がん1例を発見するのに要した費用も評価する。

副エンドポイントは、まず初回登録時における両群の胃がん検出率を評価する。さらに、観察期間内における両群の胃がん発見率とその進行度、検査終了時（6年目）の内視鏡検査における胃がん発見率とその進行度、両群におけるプロトコール以外の任意の胃検査の頻度と必要費用、両群間の死亡率減少効果の比較、各群における偶発症、である。

（2） 予定参加者

各群500人、総数1､000を目標とする。
登録期間内に予定参加者数に達しても、経過観察中の脱落等を考慮して、募集は継続することとする。

（3） 参加者数算定の根拠

必要症例数については、αエラーを0.05、パワーを0.8にして、各人にかかった費用の平均値から計算した。必要経費は、対策型胃がん検診コストは4､500円/回/人、上部消化管内視鏡検査費用は保険診療点数（D308）より11、

140円/回/人、内視鏡下生検法（D414）が3､100円/回、病理診断料（N006）は5､000円/回、ピロリ菌抗体+ペプシノゲン測定の測定費用として2､000円/回で計算した。

ピロリ菌抗体+ペプシノゲン測定・内視鏡検査群（胃がんリスク検診群）では、平均27､800円、SDは14、838円となるので、X線検査・精査内視鏡検査群（バリウム検診群）の平均31､500円との比較にこのSDを用いると、必要症例数は各群254人、全体で508人となる。なお、X線検査・精査内視鏡検査群（バリウム検診群）の要精査率を15％とした。

なお、両群ともに、今回の研究における検査以外に上部消化管内視鏡検査やレントゲン造影検査を受ける可能性がある。特にピロリ菌抗体+ペプシノゲン測定・内視鏡検査群（胃がんリスク検診群）のＡ群（ピロリ菌－、PG－）の胃がん検診が研究参加時と研究終了6年目の2回のみの上部消化管内視鏡検診のみ、通常の対策型胃がんX線検診を受ける人が多くなれば有意差が出づらくなる可能性があるので各群500人、総数1、000人と考えた。

（４） 参加者登録期間

倫理審査委員会承認後～平成25年3月31日

（５） 研究実施期間

最終参加登録後から6年間

（６） 追跡調査期間

JA秋田厚生連由利組合総合病院保健福祉活動室にてデータ保存され追跡補足可能な全期間

７．データの集積と解析

（１） 患者及びデータの取り扱い

対象者条件を満たした全ての参加登録者を本研究の対象とし、研究期間内の検査費用総額から検査 1 例あたりの平均値を主エンドポイントとする。

さらに、各群において胃がん 1 例を発見するのに要した費用の評価を副エンドポイントとする。　また、初回登録時における両群の胃がん検出率、観察期間内における両群の胃がん発見率とその進行度､検査終了時(6 年目)の内視鏡検査における胃がん発見率とその進行度、両群におけるプロトコール以外の任意の胃検査の頻度と必要費用、両群間の死亡率減少効果の比較、各群における偶発症も副エンドポイントとする。

研究および追跡期間中に他病死、及び事故などの例外的な他因死については、死亡の時点で打ちきりとして扱う。

追跡不能例は、脱落時点で打ち切りとして扱う。

（２） 登録状況の集計

定期的に、データセンターにて登録状況の集計を行い、データセンター便りとして事務局およびJA秋田厚生連由利組合総合病院保健福祉活動室に通知する。

（３） 有害事象への対応

有害事象が発生し、本研究おいて重大であると考えられたとき、対策型胃がん検診に関する新たな情報が得られた場合は直ちに国立国際医療研究センター総長に報告し、研究班員にて協議を行う。

８．予想される有害反応

本研究にて実施する検査方法は、問診のほか、通常の胃がん検診で実施しているＸ線検査、要精検と判断された場合や人間ドック等で用いられている上部消化管内視鏡検査、日常の診療の中で頻繁に行われている採血以外の方法は用いないため、それらの検査方法に通常伴う合併症以外、特段の危険は生じないものと考える。

（１） 有害事象

Ｘ線検査・精査内視鏡検査群（バリウム検診群）ではまず、Ｘ線への被曝が考えられる。しかし、半世紀にわたって実施されてきた胃がん検診でＸ線による発がん等、被曝に関するリスクを証明した疫学研究はない。バリウムを飲む際の誤嚥（特に高齢者）が考えられる。胃の集団検診受診者26万人を調査し、0.04％に起きていた、という報告もある。また、頻度は不明ながら、バリウムが原因で腸閉塞が起きることもあり、死亡事故も報告されている。

次いで、検診台からの転落の危険性がある。検診台に横たわったまま回転する等により、高齢者、とくに腕の力が衰えた女性の場合には転落して骨折したケースも報告されている。

上部消化管内視鏡検査においては、検査前に行う喉の麻酔、鎮静剤にアレルギー反応が起きたり、薬剤が効きすぎたりする可能性があるほか、検査中には、咽頭、喉頭、食道、胃などを傷つける場合も考えられる。また、生検検査に伴う出血も考えられる。日本消化器内視鏡学会による偶発症に関する全国調査（1998年～2002年）では、偶発症の頻度は0.012％と報告されている。

（２） 補償

この研究に参加した人に、参加したことによる直接の健康被害が生じた場合、当該施設は治療など適切な対応をとる。ただ特段の新たな検査方法は用いないことから、保険診療

の範囲内で対応することとし、研究費等による特別な補償措置はとらない。

本試験に参加する内視鏡医は全員、内視鏡検査事故に対する医療保険に加入することとする。

9．倫理的事項

（1） 被験者の保護

本研究の社会的な重要性・意義を踏まえながら、被験者の生命・健康・安全・プライバシー及び尊厳を保護する。研究に参加するかどうかは被験者の自由意思による。参加しなくても、そのことによる不利益は生じない。研究に参加を表明した場合でも、いつでも撤回できるし、それによる不利益は生じない。

（2） 個人情報の保護

プライバシーに関しては、血液等の検体をはじめ研究に用いるデータは厳重に管理する。本研究はヘルシンキ宣言にのっとるとともに、厚生労働省の「臨床研究に関する倫理指針」を遵守して行う。

（3） 同意の取得

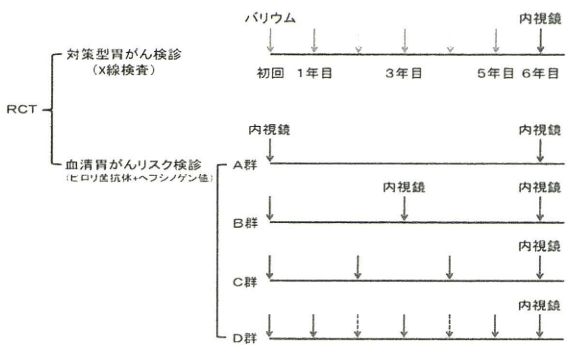
添付の説明書に基づいて説明を行い、被験者自身に、説明を受けて理解した旨を同意書に記入してもらい、署名・捺印を求める。

（4） 施設の倫理審査委員会の承認

国立国際医療研究センターの倫理委員会の審査を経るとともに、参加施設の倫理委員会の審査を経て実施する。参加施設に倫理委員会が存在しない場合は、国立国際医療研究センターの倫理委員会が一括審査を行うこともある。

C．研究結果

初年度の目標である本研究プロトコールを完成し、平成 23 年 1 月 27 日に国立国際医療研究センター倫理委員会承認（受付番号 973）された。
また、UMIN への登録も行い（UMIN 試験 ID；UMIN000005962)、研究２年目から開始する無作為割付臨床試験の準備が完了した。



D．考察

本研究は無作為割付臨床試験である。このような臨床研究計画策定に欠かせないのが計画立案とデータ管理である。そこで、平成23年度より数々の臨床研究に携わる京都府立医科大学の石川特任教授を新たに班員として迎え、試験参加者の匿名化個人情報（生年月日、性別、研究開始日時、個人連絡用登録番号）の管理、試験精度維持を担当する予定である。

E．結論

平成23年度（本研究２年目）から開始される無作為割付臨床試験において、目標とする試験参加者数の達成に向けて尽力し、科学者として研究目的の解明に努力し、最終的にはタックスペイヤーへの義務を果たしていきたい。

F．健康危険情報

報告するべき事項はない。

G．研究発表

1．論文発表

①Abe S, Oda I, Shimazu T, Kinjo T, Tada K, Sakamoto T, Kusano C, Gotoda T. Depth-predicting score for differentiated early gastric cancer. *Gastric Cancer* 14:35-40, 2011

②Nonaka S, Oda I, Nakaya T, Kusano C, Suzuki H, Yoshinaga S, Fukagawa T, Katai H, Gotoda T. Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway. *Gastric Cancer* 14:56-62, 2011

③Tanaka N, Katai H, Taniguchi H, Saka M, Morita S, Fukagawa T, Gotoda T. Trends in characteristics of surgically treated early gastric cancer patients after the introduction of gastric cancer treatment guidelines in Japan. *Gastric Cancer* 13:74-77, 2010

④Gotoda T, Iwasaki M, Kusano C, Seewald S, Oda I. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. *Br J Surg* 97:868-871, 2010

2．学会発表

報告するべき事項はない。

H．知的財産権の出願・登録状況

報告するべき事項はない。

II. 研究成果の刊行に関する一覧表

平成２２（２０１１）年 5月

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Abe S, Oda I, Shimazu T, Kinjo T, Tada K, Sakamoto T, Kusano C, Gotoda T	Depth-predicting score for differentiated early gastric cancer.	Gastric Cancer	14	35-40	2011
Nonaka S, Oda I, Nakaya T, Kusano C, Suzuki H, Yoshinaga S, Fukagawa T, Katai H, Gotoda T	Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway.	Gastric Cancer	14	56-62	2011
Tanaka N, Katai H, Taniguchi H, Saka M, Morita S, Fukagawa T, Gotoda T.	Trends in characteristics of surgically treated early gastric cancer patients after the introduction of gastric cancer treatment guidelines in Japan.	Gastric Cancer	13	74-77	2010
Gotoda T, Iwasaki M, Kusano C, Seewald S, Oda I	Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria.	Br J Surg	97	868-871	2010

III. 研究成果の刊行物・別刷り

平成２２（２０１１）年　5月

Gastric Cancer
DOI 10.1007/s10120-011-0002-z

ORIGINAL ARTICLE

Depth-predicting score for differentiated early gastric cancer

Seiichiro Abe · Ichiro Oda · Taichi Shimazu · Tetsu Kinjo · Kazuhiro Tada · Taku Sakamoto · Chika Kusano · Takuji Gotoda

Received: 31 March 2010 / Accepted: 24 August 2010

Abstract
Background Intramucosal and minute submucosal (M-SM1; <500 μm in depth) differentiated gastric cancers, which have a negligible risk of lymph node metastasis, are the targets for endoscopic resection. However, there have been few reports about the endoscopic distinction between these cancers and cancers with deeper submucosal invasion (SM2; ≥500 μm in depth). The aim of this retrospective study was to analyze the differences in the endoscopic features between M-SM1 and SM2 cancers, and to develop a simple scoring model to predict the depth of these early gastric cancers.
Methods We analyzed 853 differentiated early gastric cancers treated endoscopically or surgically as a derivation group. Endoscopic images were reviewed to determine the relationship between depth of invasion and the following endoscopic features: tumor location, macroscopic type, tumor size, and endoscopic findings (remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds). Secondly, we created a depth-predicting model based on the obtained data and applied the model to 211 validation samples.
Results On logistic regression analysis, tumor size more than 30 mm, remarkable redness, uneven surface, and margin elevation were significantly associated with deeper submucosal cancers. A depth-predicting score was created by assigning 2 points for margin elevation and tumor size more than 30 mm, and 1 point for each of the other endoscopic features. When validation lesions of 3 points or more were diagnosed as deeper submucosal cancers, the sensitivity, specificity, and accuracy as evaluated by three endoscopists were 29.7–45.9, 93.1–93.7, and 82.5–84.8%, respectively.
Conclusions The depth-predicting score could be useful in the decisions on treatment strategy for differentiated M-SM1 early gastric cancers.

Keywords Early gastric cancer · Depth · Diagnosis · Endoscopy

S. Abe · I. Oda (✉) · T. Kinjo · K. Tada · T. Sakamoto · C. Kusano · T. Gotoda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ioda@ncc.go.jp

T. Shimazu
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

C. Kusano · T. Gotoda
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan

Introduction

Endoscopic resection in patients with early gastric cancer (EGC) is less invasive and more economical than conventional surgery. The negligible incidence of lymph node metastasis in certain stages of EGC means that, in selected cases, patients can be cured with such therapies. Gotoda et al. [1] concluded that among 5265 patients who underwent gastrectomy, there was no lymph node involvement in differentiated mucosal (M) gastric cancers without lymphatic or vessel invasion when the cancers were smaller than 3 cm in diameter with ulceration, or any size without ulceration. Differentiated minute submucosal (SM1, <500 μm in depth) cancers without lymphatic or venous involvement and cancers smaller than 3 cm also showed no lymph node involvement [1]. The endoscopic submucosal dissection (ESD) technique using an insulation-tipped

Published online: 17 February 2011

diathermic knife or other endo-knives could technically achieve one-piece resection for such lesions [2–7]. It is important to distinguish M-SM1 cancers from deeper submucosal (SM2; ≥500 μm in depth) cancers, which have the possibility of lymph node metastasis, for making the proper decision on treatment strategy.

Thus, preoperative determination of the depth of invasion is important. Although the usefulness of endoscopic ultrasonography (EUS) has been reported, with this modality it is impossible to distinguish M-SM1 from SM2 definitively [8, 9]. Conventional endoscopy is the initial route of EGC detection, but there have been few reports comparing the endoscopic features of EGC stages M-SM1 and SM2. Furthermore, no objective criteria regarding the depth of invasion exist, and many endoscopists diagnose based on their own experiences. The aim of this retrospective study was to analyze the differences in the endoscopic features between M-SM1 and SM2, and to develop a simple model to predict the depth of these EGCs.

Materials and methods

Analyzed lesions and review methods

A total of 880 consecutive differentiated EGCs were treated endoscopically or surgically between 2001 and 2003 at the National Cancer Center Hospital in Tokyo. Twenty-seven lesions were excluded because precise endoscopic findings could not be depicted [eight detected in remnant stomach, six after esophagectomy, six local recurrences after endoscopic mucosal resection (EMR), five with insufficient endoscopic images, one with a tattoo, and another with an endo-clip artifact].

The remaining 853 differentiated EGCs (M 592, SM1 111, SM2 150, mean patient age of 65.6 years, 686 male and 167 female patients) were analyzed as a derivation group. An endoscopist (S.A.), experienced with more than 5000 gastroscopies, reviewed conventional endoscopic images without histological information about depth. The following characteristics were evaluated: tumor location (upper, middle, and lower), tumor size (mm), macroscopic type, and five other endoscopic findings that are widely accepted as markers of deeper submucosal invasion among Japanese endoscopists, with some minor variations (remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds) [10, 11].

Subsequently, we made a simple and practical scoring model (depth-predicting score, DPS) to distinguish M-SM1 from SM2 cancers, based on the analyzed data in the derivation group. Three endoscopists (S.A., T.K., and K.T., each experienced with more than 5000 gastroscopies) evaluated the endoscopic findings and investigated the sensitivity, specificity, and accuracy of our DPS in our validation set, consisting of 211 differentiated EGCs treated between January and June in 2000 at our hospital.

Conventional white-light endoscopy (video-endoscope Q240 or Q260; Olympus Medical Systems, Tokyo, Japan) was used for pretreatment endoscopic examination. In addition, surface details were enhanced by indigo-carmine chromoendoscopy.

Definitions

The EGC macroscopic and histological types in the enrolled patients were decided according to the *Japanese classification of gastric carcinoma* [12]. We divided the macroscopic types into three groups: IIa (elevated lesions such as 0 I, 0 IIa, and 0 I + IIa), IIc (depressed lesions such as 0 IIc, 0 IIc + III, and 0 III + IIc), and IIa + IIc (combined type, such as 0 IIa + IIc and 0 IIc + IIa). Histological type was diagnosed based on the predominant tumor pattern and then divided into two types; differentiated type and undifferentiated type. Well differentiated, moderately differentiated, and papillary adenocarcinoma were defined as differentiated type.

We described five endoscopic features in this study. Remarkable redness was defined as a reddish area similar to regenerative epithelium (Fig. 1). Nodulations in the tumor's surface were considered an uneven surface (Fig. 2). Margin elevation referred to the finding of a protruding edge surrounding the tumors, including submucosal tumor like component with a limited amount of air insufflation (Fig. 3a, b). Either a scar or an ulcerative area within the tumors was evaluated as ulceration (Fig. 4). Finally, enlarged folds included any thickened or merged convergent folds (Fig. 5).

Statistical methods

To identify the variables that were significantly more common in SM2, the endoscopic data were initially

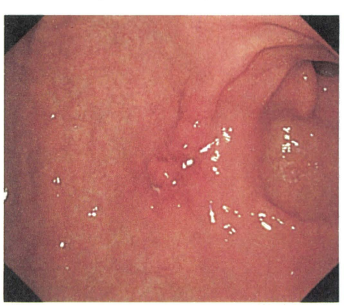


Fig. 1 Remarkable redness: endoscopic picture shows unusual redness inside the lesion

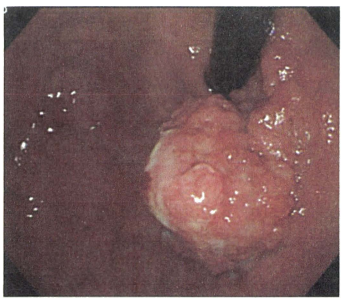


Fig. 2 Uneven surface: nodular mucosa can be seen

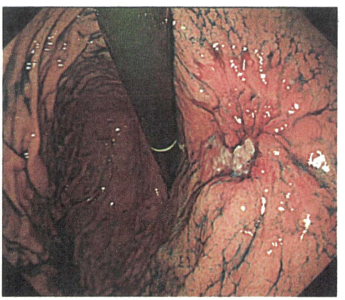


Fig. 4 Ulceration: endoscopic picture of ulceration

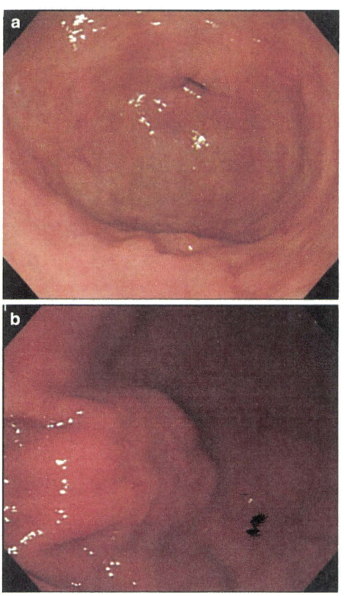


Fig. 3 **a** Margin elevation: endoscopic picture of surrounding elevation. **b** Margin elevation: endoscopic picture of submucosal tumor like component can be demonstrated from the view with a limited amount of air insufflation

evaluated with Student's t test for tumor size and the χ^2 test for other endoscopic features. We then entered the candidate variables into a logistic regression analysis.

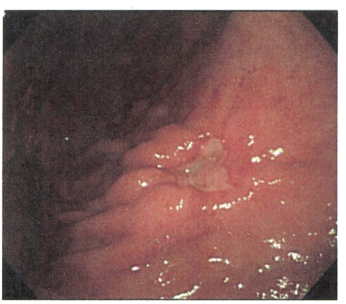


Fig. 5 Enlarged folds: thickened or merged folds can be seen toward the inside of the lesion

Endoscopic features independently and statistically associated with SM2 penetration were selected as examination items for the DPS. The relative weighting of each DPS variable was based on its β-coefficient in the logistic regression analysis. The significance level was set at 5% for each analysis. A p value of <0.05 was considered significant.

Results

Analysis of endoscopic features

Table 1 shows the histological and therapeutic characteristics of both the derivation and validation groups. There were no significant differences between the two groups in the depth of invasion, histological type, or treatment strategies.

Table 1 Histological and therapeutic characteristics

	Derivation group ($n = 853$)	Validation group ($n = 211$)	p value
Depth (M-SM1/SM2)	703/150	175/36	NS*
Histological type			
Well	732	185	NS*
Moderately	109	25	
Papillary	12	1	
Treatment			
EMR/ESD	632	171	NS*
Surgery	221	40	

M-SM1 intramucosal and minute submucosal (<500 μm in depth) cancers, *SM2* deeper submucosal (≥500 μm in depth) cancers, *well* well-differentiated adenocarcinoma, *moderately* moderately differentiated adenocarcinoma, *papillary* papillary adenocarcinoma, *EMR*, endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *NS* not significant

* χ^2 test

Table 2 Endoscopic comparison between M-SM1 and SM2 in derivation group

	M-SM1 ($n = 703$)	SM2 ($n = 150$)	p value
Location			
U	134	38	
M	257	35	NS*
L	312	77	
Tumor size (mm)			
Mean, range	19.2 (3–120)	31.6 (5–120)	<0.0001**
Macroscopic type			
IIa	178	30	
IIc	458	88	
IIa + IIc	67	32	<0.0001*
Endoscopic features			
Remarkable redness	160 (22.8%)	70 (46.7%)	<0.0001*
Uneven surface	72 (10.2%)	47 (31.3%)	<0.0001*
Margin elevation	110 (15.6%)	82 (54.7%)	<0.0001*
Ulceration	152 (21.6%)	57 (38.0%)	<0.0001*
Enlarged folds	7 (1.0%)	11 (7.3%)	<0.0001*

U upper, *M* middle, *L* lower

* χ^2 test, ** Student's t test

In the derivation group, there was no significant difference in tumor location between M-SM1 and SM2. SM2 gastric cancers were significantly larger and were characterized as IIa + IIc. According to the endoscopic features, we also found statistically significant differences in remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds (Table 2).

The tumor size cutoff was set at 30 mm with a cross point between the receiver operating characteristic (ROC) curve against SM2 and the 45° line, which represented the ROC curve of a test whose decision ability is no better than chance (Fig. 6). Tumor size more than 30 mm was determined as a variable in multivariate analysis.

In the logistic regression analysis, tumor size (more than 30 mm), macroscopic type, and endoscopic features which were significantly more common in SM2 by univariate analysis were investigated. As a result, margin elevation, tumor size (more than 30 mm), remarkable redness, and uneven surface were significantly associated with SM2 EGCs (Table 3).

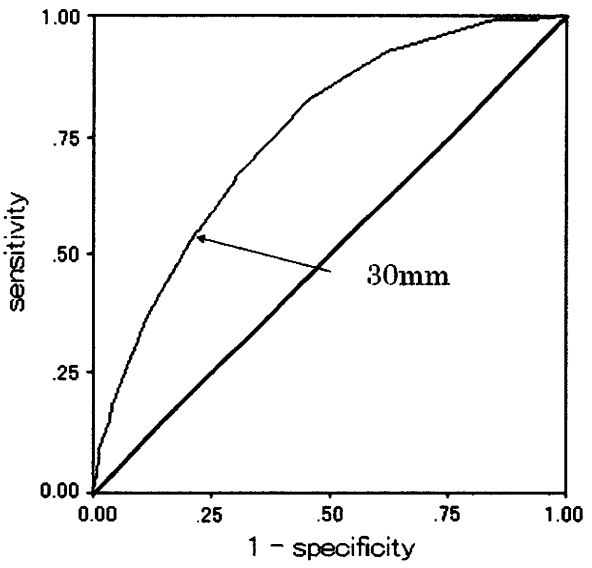


Fig. 6 Receiver operating characteristic curve for tumor size and the sensitivity of submucosal cancers ≥500 μm in depth (SM2): the *arrow* (30-mm diameter) shows the cutoff point between intramucosal and minute submucosal <500 μm in depth (M-SM1) and SM2 cancers

Establishment of depth-predicting score

The DPS was created based on the above results. One point was given for remarkable redness and uneven surface, while margin elevation and tumors more than 30 mm were scored with 2 points because the relative magnitude of the β-coefficient was roughly twice that of other variables. Thus, the range of the resulting DPS was 0–6 points (Table 4). A total of 3 points was defined as the cutoff between M-SM1 and SM2. This was done in order to balance the power for SM2 selection and minimize the population for overtreatment. The sensitivity, specificity, and accuracy of the proposed DPS were 57.3% (95% confidence interval [CI] 49.4–65.3%), 86.2% (95% CI

Table 3 Multivariate logistic regression analysis

	β-coefficient	Odds ratio (95% CI)	p value
Margin elevation	7.838	6.221 (3.938–9.825)	<0.0001
Tumor size (more than 30 mm)	6.570	4.937 (3.066–7.951)	<0.0001
Remarkable redness	3.411	2.087 (1.367–3.186)	0.0006
Uneven surface	3.343	2.306 (1.413–3.764)	0.0008

CI confidence interval

Evaluated items in multiple logistic regression analysis were followed: tumor size more than 30 mm, macroscopic type (IIa + IIc), remarkable redness, uneven surface margin elevation, ulceration and enlarged folds. Only the statistically significant items are listed in the table

Table 4 Proposed depth-predicting score

Factor	Points	
	Present	Absent
Margin elevation	2	0
Tumor size (more than 30 mm)	2	0
Remarkable redness	1	0
Uneven surface	1	0

83.7–88.8%), and 81.1% (95% CI 78.5–83.8%), respectively (Fig. 7).

Finally, we applied the suggested DPS model to the 211 validation lesions without any histological information. When we considered 3 points or more as SM2, the sensitivity, specificity, and accuracy of the proposed DPS, assigned by the three endoscopists, were 29.7–45.9, 93.1–93.7, and 82.5–84.8%, respectively. When we divided the validation group into "IIa" and "IIc/IIa + IIc", the sensitivity, specificity, and accuracy were 50.0–83.3, 92.6–96.3, and 91.7% (by all three endoscopists) for IIa lesions and 25.8–38.7, 92.5–93.3, and 78.8–82.1% for IIc/IIa + IIc lesions (Table 5).

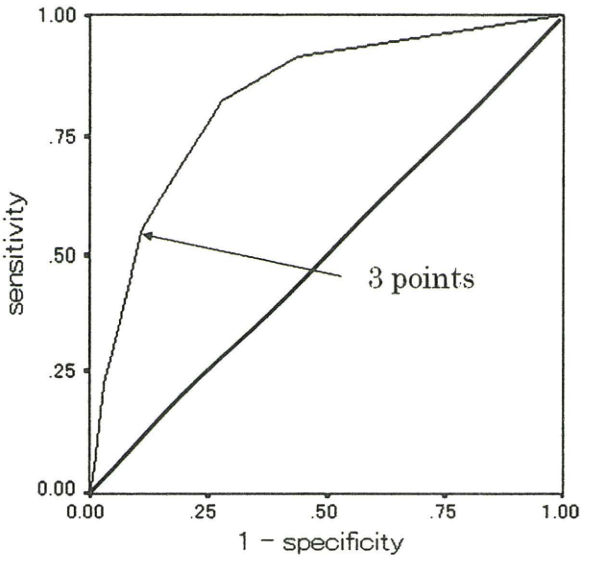


Fig. 7 Receiver operating characteristic curve for depth-predicting score (DPS) and the sensitivity of SM2: the *arrow* (3 points) shows the cutoff point between M-SM1 and SM2

Table 5 Diagnostic sensitivity and specificity by depth-predicting score according to macroscopic type in the validation group

	IIa	IIc/IIa + IIc	Total
Endoscopist 1			
Sensitivity	50.0% (3/6)	25.8% (8/31)	29.7% (11/37)
Specificity	96.3% (52/54)	92.5% (111/120)	93.7% (163/174)
Accuracy	91.7% (55/60)	78.8% (119/151)	82.5% (174/211)
Endoscopist 2			
Sensitivity	83.3% (5/6)	38.7% (12/31)	45.9% (17/37)
Specificity	92.6% (50/54)	93.3% (112/120)	93.1% (162/174)
Accuracy	91.7% (55/60)	82.1% (124/151)	84.8% (179/211)
Endoscopist 3			
Sensitivity	50.0% (3/6)	35.8% (11/31)	37.8% (14/37)
Specificity	96.3% (52/54)	92.5% (111/120)	93.7% (163/174)
Accuracy	91.7% (55/60)	80.8% (122/151)	83.9% (177/211)

Discussion

Patients' quality of life is one of the most important issues in EGC treatment, because the prognosis of EGC is favorable [13]. Differentiating endoscopically resectable M-SM1 gastric cancers from surgically resectable SM2 lesions is of great significance, given the low risk of lymph node metastases with the former. In conventional endoscopic diagnosis for these EGCs, however, endoscopists have had to empirically estimate the depth of invasion, as no objective criteria existed.

The first aim of this retrospective study was to analyze the differences in conventional endoscopic features between M-SM1 and SM2 EGCs. We found that tumor size more than 30 mm, margin elevation, uneven surface, and remarkable redness were significantly associated with an increased risk of SM2 invasion according to logistic regression analysis.

There have been few reports about the usefulness of conventional endoscopy for predicting depth of invasion. The overall accuracy rates for determining depth of invasion of EGCs were between 63 and 73% by non-objective criteria [11, 14, 15]. Namieno et al. [16] concluded that

macroscopic appearance, histological differentiation, and tumor size were associated with submucosal invasion. However, they did not analyze the morphologic features of the tumors.

Although we used endoscopy in the present study, EUS can also show the depth of invasion clearly. The introduction of high-frequency thin probes has allowed target scanning with high resolution under endoscopic control [8, 9]. In spite of some excellent accuracy data [17], there have been no significant differences between EUS and endoscopy in terms of depth accuracy [14].

Considering the need for simple and objective diagnosis, we proposed an endoscopic determination for the depth of invasion of differentiated EGCs by the DPS described here, based on our analysis of the derivation group. The DPS could be used to determine an appropriate treatment strategy for the validation group with 82.5–84.8% accuracy. Based on macroscopic type, the accuracy for elevated lesions tended to be better than that for the depressed and combined lesions.

Although specificity was good in steering M-SM1 cancers toward endoscopic treatment, low sensitivity was a weak point of the DPS. Selected endoscopic features may not reflect microscopic SM2 invasion. Also, each variable was considered as only either present or absent. If the significance of each finding had been taken into consideration, the sensitivity and accuracy of the score may have increased. However, this would have complicated the DPS, and was therefore not done.

EUS could be omitted for lesions with a DPS of less than 2 points and endoscopic resection performed, except for large ulcerative lesions more than 30 mm in diameter. Lesions with a DPS of 3 points or more may be considered as candidates for additional EUS, potentially providing more precise prediction. By using this simple diagnostic model, appropriate treatment strategies can be determined for differentiated M-SM1 EGCs, while saving time and cost as compared to EUS being done for all cases.

The limitation of this investigation was the retrospective design at a single institution. Further research in a prospective study is needed to investigate the utility of the DPS in combination with EUS for lesions with a DPS of 3 points or greater.

In conclusion, the proposed DPS may be useful in making treatment decisions for differentiated M-SM1 EGCs.

Acknowledgments The authors had the generous support and encouragement of Dr. Hitoshi Kondo (The Center for Digestive Diseases, Tonan Hospital, Japan). Also, we wish to thank Dr. Jeffery Paul Gaboury (Department of Surgery, University of Saskatchewan, Canada) and Dr. Satchan Takaya (Division of Infectious Diseases, University of Saskatchewan, Canada) for correcting the English used in this manuscript.

References

1. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer. 2000;3:219–25.
2. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut. 2001;48:225–9.
3. Oyama T, Kikuchi Y. Aggressive endoscopic mucosal resection in the upper GI tract. Hook knife EMR method. Minim Invasive Ther Allied Technol. 2002;11:291–5.
4. Yahagi N, Fujishiro M, Kakushima N, Kobayashi K, Hashimoto T, Oka M, et al. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). Dig Endosc. 2004;16:34–8.
5. Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, et al. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy. 2003;35:690–4.
6. Ono H, Hasuike N, Inui T, Takizawa K, Ikehara H, Yamaguchi Y, et al. Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. Gastric Cancer. 2008;1:47–52.
7. Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer. 2006;9:262–70.
8. Ohashi S, Segawa K, Okamura S, Mitake M, Urano H, Shimodaira M, et al. The utility of endoscopic ultrasonography and endoscopy in the endoscopic mucosal resection of early gastric cancer. Gut. 1999;45:599–604.
9. Ichikawa T, Kudo M, Matsui S, Okada M, Kitano M. Endoscopic ultrasonography with three miniature probes of different frequency is an accurate diagnostic tool for endoscopic submucosal dissection. Hepatogastroenterology. 2007;54:325–8.
10. Ono H, Yoshida Y. Endoscopic diagnosis of the depth of cancer invasion for gastric cancer. Stomach Intest. 2001;36:334–40. (in Japanese with English abstract).
11. Sano T, Okuyama Y, Kobori O, Shimizu T, Morioka Y. Early gastric cancer endoscopic diagnosis of depth of invasion. Dig Dis Sci. 1990;35:1340–4.
12. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer. 1998; 1:10–24.
13. Sasako M, Kinoshita T, Maruyama K. Prognosis of early gastric cancer. Stomach Intest. 1993;28(Suppl):139–46. (in Japanese with English abstract).
14. Yanai H, Noguchi T, Mizumachi S, Tokiyama H, Nakamura H, Tada M, et al. A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. Gut. 1999;44:361–5.
15. Shirao K, Saito D, Yamaguchi H, Shirato M, Fukuda H, Yoshida S. Accuracy of preoperative diagnosis of early gastric cancer on submucosal invasion: a study for indication of endoscopic treatment. Stomach Intest. 1992;27:1175–83. (in Japanese with English abstract).
16. Namieno T, Koito K, Hiigashi T, Takahashi M, Shimamura T, Yamashita K, et al. Endoscopic prediction of tumor depth of gastric carcinoma for assessing the indication of its limited resection. Oncol Rep. 2000;7:57–61.
17. Yoshida S, Tanaka S, Kunihiro K, Mitsuoka Y, Hara M, Kitadai Y. Diagnostic ability of high-frequency ultrasound probe sonography in staging early gastric cancer, especially for submucosal invasion. Abdom Imaging. 2005;30:518–23.

Gastric Cancer
DOI 10.1007/s10120-011-0008-6

ORIGINAL ARTICLE

Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway

Satoru Nonaka · Ichiro Oda · Teruo Nakaya · Chika Kusano · Haruhisa Suzuki · Shigetaka Yoshinaga · Takeo Fukagawa · Hitoshi Katai · Takuji Gotoda

Received: 16 June 2010 / Accepted: 30 September 2010

Abstract
Background Endoscopic submucosal dissection (ESD) is a technique developed to enable the endoscopic resection (ER) of large and ulcerative neoplastic lesions that were previously unresectable using conventional endoscopic mucosal resection (EMR). We investigated the clinical outcomes of ER of early gastric cancer (EGC) before and after the introduction of ESD, with particular attention to surgery and its potential consequences.
Methods We reviewed 2,785 consecutive surgical patients with EGC and 2,469 consecutive lesions treated by ER with curative intent between 1990 and 2005. The study was divided into an EMR period (1990–1999) and an ESD period (2000–2005). We analyzed the clinical outcomes of endoscopic and surgical resections and defined 'potentially avoidable surgery' as cases of surgery performed for lesions curable by ER.
Results The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ($P < 0.001$). For ER patients, the rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group ($P < 0.001$). The rate of non-curative ER for lesions defined as having 'positive or difficult to estimate horizontal margins only' decreased significantly, from 26.1% (109/417) in the EMR group to 1.4% (29/2,052) in the ESD group ($P < 0.001$). Conversely, the rate of non-curative ER for lesions defined as having 'possible lymph node metastasis' significantly increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ($P < 0.01$).
Conclusions The application of a pathway involving ESD resulted in a significant decrease in the rate of potentially avoidable surgery, highlighting the advantages associated with performing ESD.

Keywords Early gastric cancer · Lymph node metastasis · Endoscopic submucosal dissection · Potentially avoidable surgery · Non-curative endoscopic resection

Abbreviations

ER	Endoscopic resection
EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
sm2	Submucosal deep invasion
sm1	Submucosal superficial invasion

Introduction

Therapeutic endoscopic resection (ER) has been performed for early gastric cancer (EGC) since the mid 1980s and is now accepted as the standard treatment for those patients with negligible risk of lymph node metastasis [1–8]. The conventional method by which EGCs were removed was by endoscopic mucosal resection (EMR). The limitations

S. Nonaka · I. Oda (✉) · T. Nakaya · C. Kusano · H. Suzuki · S. Yoshinaga · T. Gotoda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ioda@ncc.go.jp

C. Kusano · T. Gotoda
Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan

T. Fukagawa · H. Katai
Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Published online: 17 February 2011

of applying EMR to all potentially endoscopically resectable lesions were size, location, and scarring from previous ulceration, so that only piecemeal removal was possible in such cases [9–11]. Unfortunately, piecemeal resection of EGC is associated with both difficulties in accurate histological assessment and a higher rate of local recurrence [12, 13]. Consequently, surgery was often chosen as the initial preferred method of treatment for lesions which were difficult to resect by EMR and those associated with difficulty in estimation of tumor depth.

A major breakthrough was achieved at the turn of the twenty-first century, with the advent of endoscopic submucosal dissection (ESD) [14–20]. ESD is a technique developed to enable the resection of large and ulcerative lesions, regardless of tumor location, that are unable to be removed using the conventional EMR procedure. The other major advantage of ESD is its ability to achieve a higher rate of en-bloc resection, thus providing more accurate histological assessment as compared to EMR [12, 21]. For the aforementioned reasons, ESD has translated into lower rates of local recurrence of gastric cancer as compared with EMR [22, 23]. The gastric cancer treatment guidelines of the Japanese Gastric Cancer Association for lesions that are considered curative by EMR are shown in Table 1 [24]. Based on the risk of lymph node metastasis determined from a large cohort of surgically treated cases of EGCs, ESD is now regarded as a curative procedure for lesions selected using the National Cancer Center expanded criteria (Table 2) [25].

Table 1 JGCA guideline criteria for endoscopic resection

Differentiated adenocarcinoma
Intramucosal cancer
≤20 mm in size without ulceration

JGCA Japanese Gastric Cancer Association

Table 2 NCC expanded histopathological criteria for curative endoscopic resection

Early gastric cancer with negligible risk of lymph node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumor size without ulceration
Or intramucosal cancer ≤30 mm in size with ulceration
Or submucosal superficial cancer (sm1) ≤30 mm in size
Resection margin
Tumor-free horizontal margin
Tumor-free vertical margin

NCC National Cancer Center

An important advantage of ESD is that it can also be considered as improving diagnostic assessment due to the suboptimal accuracy of the endoscopic staging of EGC, which is sometimes difficult because EGC shows unclear margins due to gastritis, and depth diagnosis is not always accurate [26–28]. Thus, the use of ESD has enabled us to achieve enhanced diagnosis of lesions where it may have been difficult to estimate the tumor depth or where there was a technical difficulty in resection with EMR. The treatment strategy in which additional surgery is performed after confirmation of the histological assessment of the ER specimen has already been established as one of the therapies for EGC [29–31]. We hypothesized that ESD might reduce the rate of potentially avoidable surgery by its improvement of diagnostic and therapeutic capacity compared to that of EMR. We retrospectively investigated the relationship between the surgical and endoscopic treatment of EGC before and after the introduction of ESD, with particular attention to the rate of surgical resection and its potential consequences.

Patients and methods

We retrospectively reviewed the clinical records and endoscopic and histological reports of 2,785 consecutive patients with EGC treated by surgery with curative intent and 3,102 consecutive EGC lesions treated by ER at the National Cancer Center Hospital, Tokyo, between 1990 and 2005. Informed consent was obtained from all patients in accordance with the institutional protocol. Our primary aim in this study was to retrospectively compare the rate of potentially avoidable surgery before and after the introduction of ESD and to compare the rates of non-curative ER and rates of complications between the EMR and ESD groups. All patients and lesions were discussed and the treatment strategies were determined in weekly multidisciplinary conferences involving endoscopists, surgeons, radiologists, and pathologists. The study was divided into an EMR period (1990–1999), during which the main endoscopic modality of treatment for EGC was EMR, based on the guideline criteria of the Japanese Gastric Cancer Association (Table 1) [24] and an ESD period (2000–2005), during which ESD became the predominant method by which EGCs were endoscopically resected, based on the National Cancer Center expanded criteria (Table 2) [25].

For surgical patients, we defined cases of 'potentially avoidable surgery' as those cases with surgically resected histopathological specimens within the guideline criteria of the Japanese Gastric Cancer Association [24]. In other words, the patients with potentially avoidable surgery were those who underwent surgery for lesions curable by ER.

In the ER patients, 2,469 lesions, after exclusions, were treated by ER with curative intent; 417 lesions from the EMR group included only those lesions that were treated by EMR during the EMR period, while 2,052 lesions from the ESD group involved only those lesions that were treated by ESD during the ESD period. Another 248 lesions that were treated by ESD in the EMR period and 90 lesions that were treated by EMR in the ESD period, all with curative intent, were excluded from this study (Fig. 1). In addition, other EGCs were excluded from this study because ERs were performed for palliative purposes or because the ERs were performed for residual/recurrent lesions from previous endoscopic treatments. Palliative ERs were performed in patients who refused or were unfit for surgery because of comorbidities and for those lesions found during pre-therapeutic staging to have submucosal deep invasion (sm2) or deeper invasion, as well as those lesions with undifferentiated adenocarcinomas as revealed by biopsies. Palliative ERs included 191 lesions (150 by ESD and 41 by EMR) and residual/recurrent ERs included 104 lesions (100 by ESD and four by EMR) during each respective period (Fig. 1).

The curability of ER was divided into categories of curative and non-curative; the non-curative category included lesions that could not be precisely evaluated histologically based on the National Cancer Center expanded criteria and the tumor margins [25]. Non-curative ER was separated into two groups based on histological results: 'non-curative with positive or difficult to estimate horizontal margins only' and 'non-curative with a possible risk of lymph node metastasis irrespective of horizontal margin', based on submucosal deep invasion (sm2: ≥500 μm), positive lymphatic and/or venous invasion, intramucosal cancer more than 3 cm in size in the presence of ulceration, submucosal superficial invasion (sm1: <500 μm) in a lesion greater than 3 cm in size, predominantly undifferentiated type adenocarcinoma, and positive vertical margin (Table 3). Therefore, non-curative ERs with a possible risk of lymph node metastasis were cases of ER carried out in patients who went on to require additional surgery. In other words, these patients were those who underwent ER for lesions curable by surgery. Complications including perforation and delayed bleeding that required blood transfusion were also investigated in the EMR and ESD groups.

Clinical outcomes were analyzed using the χ^2 test and Fisher's exact test (Statview; Abacus Concepts, Berkeley, CA, USA), and $P < 0.05$ was considered statistically significant.

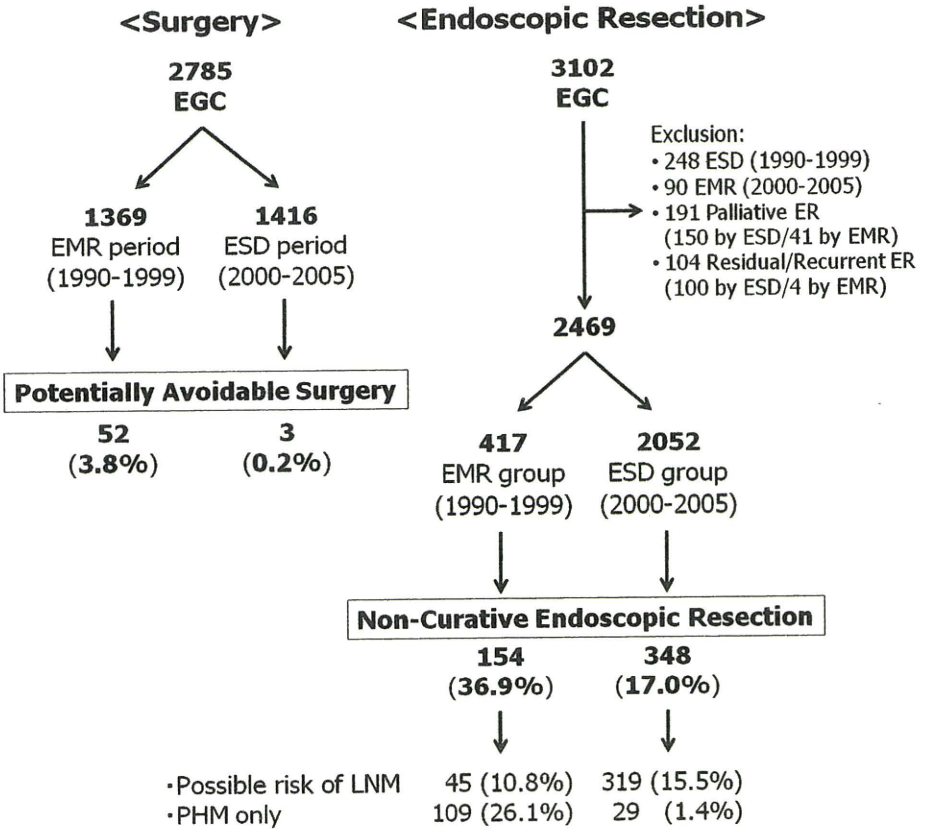


Fig. 1 Outline of the study, including rates of potentially avoidable surgery and non-curative endoscopic resection based on the histological results. *EGC* Early gastric cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin