## 11. QOL 調査票回収状況

QOL 調査参加施設:国立がん研究センター中央病院、神奈川県立がんセンター、静岡県立静岡がんセンター、愛知県がんセンター中央病院

2012 年 4 月 6 日現在

| 全調査対象 384 例 | 登録時 | 術後 30 日 | 術後 90 日 | 術後 1 年 | 術後 3 年 |
|---|---|---|---|---|---|
| | | 調査予定日前 20 例 | 調査予定日前 60 例 | 調査予定日前 182 例 | 調査予定日前 382 例 |
| | 回収済み 377 例 | 回収済み 354 例 | 回収済み 319 例 | 回収済み 193 例 | 回収済み 0 例 |
| | 未回収 6 例 | 未回収 7 例 | 未回収 2 例 | 未回収 6 例 | 未回収 0 例 |
| | 回収不能 1 例 | 回収不能 1 例 | 回収不能 1 例 | 回収不能 1 例 | |
| | 依頼せず 0 例 | 依頼せず 2 例 | 依頼せず 2 例 | 依頼せず 2 例 | 依頼せず 2 例 |

QOL 調査事務局からの報告

| No. | 調査時期 | 調査票 | コメント |
|---|---|---|---|
| 45 | 術後 30 日 | 回収不能 | 記入・投函されたが、郵送段階で行方不明 |
| 49 | 登録時 | 回収不能 | 患者拒否*1 |
| | 術後 30 日 | 依頼せず | 登録時 QOL 調査欠損(患者拒否)のため |
| | 術後 90 日 | | |
| | 術後 1 年 | | |
| | 術後 3 年 | | |
| 195 | 術後 30 日 | 依頼せず | 臨床試験に対する家族の理解が得られなくなった |
| | 術後 90 日 | | |
| | 術後 1 年 | | |
| | 術後 3 年 | | |

*1【データセンターコメント】A 群に割り付けられたが患者拒否あり。腹腔鏡下手術施行

CRF で「依頼できなかった」と報告された症例(調査予定日前に CRF が回収された症例を含む)

| No. | 調査時期 | コメント |
|---|---|---|
| 8 | 術後 1 年 | 外来日が調査日より遠い為、返送(郵送)されず、電話(留守電)と葉書により督促したが返事がない |
| 195 | 術後 30 日 | 家族の臨床試験に対する協力が得られなくなりアンケート調査を主治医の判断で中止とする |
| | 術後 90 日 | 術後合併症により入院が長引き、試験に対する家人の協力が得られず QOL 調査は中止となる |

# 資料　6

JCOG 効果・安全性評価委員会　御中

2012 年 2 月 8 日

平素より大変お世話になっております。

JCOG 0912「臨床病期 I 期胃癌に対する腹腔鏡下幽門側胃切除術の開腹幽門側胃切除に対する非劣性を検証するランダム化比較試験」プロトコール改訂案を提出致します。

改訂理由については、それぞれのプロトコール改訂箇所に記しております。

ご審議の程、宜しくお願い申し上げます。

改訂事項

1) 中間解析時期の変更
2) 適格規準の変更
3) 胃癌取扱い規約第14版、胃癌治療ガイドライン第3版の追記
4) リンパ節郭清の規定の追記
5) プロトコール治療中止規準の追記
6) 有害事象項目の追加
7) 術者認定申請書の送付先の補完
8) 定型章および研究者情報の更新
9) IC文書の更新（グループ名・研究費名等の更新）

JCOG 胃がんグループ代表者

兵庫医科大学　笹子三津留

JCOG 0912 研究代表者/研究事務局

国立がん研究センター中央病院　片井　均

**○改訂箇所 1：中間解析時期の変更**

2012 年 1 月末現在の登録数は 478 名となっています。第 1 回中間解析は、予定登録数（920 名）の半数（460 名）が登録された次のモニタリングのデータを用いて実施する予定であり、2012 年前期モニタリングのデータを用いて、登録期間中の中間解析を実施することになります。

しかし、2011 年度前期定期モニタリングレポートでの primary endpoint である全生存期間のイベントの発生はなく、現在実施中の、2011 年度後期定期モニタリングにても、イベントの発生はほとんどおこらないことが見込まれます。イベント数がゼロの状況ですので、2011 年度後期定期モニタリングレポートのタイミングでの中間解析は実施しない方針としたいと思います。

本来、予定された登録数まで患者登録を続けてよいかどうかを検討するために、無効中止を検討する中間解析を登録中に一回は実施するべきですが、登録中には全生存期間のイベントがほとんど生じないことが予想されます。そのため、代わりに無再発生存期間により、無効中止を検討するための中間解析を実施する旨の記載に変更いたしました。ただし、無再発生存期間のイベント数も 2011 年前期の時点で 1 例のみであり、登録中に中間解析を行えるほどの無再発生存期間のイベント数が観察されるかどうかは微妙な状況です。よって、登録期間中に両群合わせて無再発生存期間のイベント数が 20 例に達した場合は、無効中止を検討するための中間解析を実施し、登録期間中に無再発生存期間のイベントが 20 例未満の場合は、登録中の中間解析は行わないこととといたしました（10 例程度では 1、2 例のイベント発現状況の違いで結果の解釈が大きく変わってしまう可能性があることから、あくまで大まかな目安ですが 20 例といたしました）。

なお、本試験の対象である比較的早期の胃癌では術後数年たってから再発する場合も多いため、現時点で当初の想定より予後がよいかどうかの判断は困難です。当初の想定より実際の予後が良かった場合にはサンプルサイズの上方修正や追跡期間の延長などを検討する必要がありますが、登録終了直前のモニタリングレポートのタイミングで、こうした修正が必要かどうかを検討したいと思います。

**12.3.1. 中間解析の目的と時期**

試験の途中で本試験の主たる目的が達成されたかどうかを判断する目的で 2 回の中間解析を行う。1 回目の中間解析は、登録中に登録を続けることが妥当かどうかを判断する目的で、2 回目の中間解析は登録終了後早期に、予定した期間の追跡を続けるかどうかを判断する目的で行う。いずれの場合も試験の主たる目的が達成されていると判断された場合は試験を中止し、速やかに試験結果を学会及び論文にて公表する。

1 回目の中間解析は、予定登録数の半数の登録が得られた時点以降に問い合わせを行う最初の定期モニタリングのデータを用いて行い、2 回目の中間解析は、登録が終了し、すべての登録患者のプロトコール治療が終了する時期を目途に、データセンターと研究代表者/研究事務局で相談した上で適切と思われる時期の定期モニタリングに合わせて行う。原則として中間解析中も登録は停止しない。

＜v1.2 での追記事項＞

1 回目の中間解析は、予定登録数の半数の登録が得られた時点以降の最初の定期モニタリングのタイミングである 2011 年度後期モニタリングのデータを用いて行う予定であったが、2011 年度前期の時点で全生存期間のイベント数がゼロであったため、2011 年度後期モニタリングのタイミングでは中間解析は行わないこととした。

登録終了までに中間解析が行えるほどの全生存期間のイベント数が得られないことが予想されるため、1 回目の中間解析は無再発生存期間を用いて行う。ただし、登録中に中間解析が行えるほどの無再発生存期間のイベント数が観察されるかどうかは不明であるため、登録期間中に両群合わせて無再発生存期間のイベント数が 20 例に達した場合は、無効中止を検討するための中間解析を実施し、登録期間中に無再発生存期間のイベントが 20 例未満の場合は、登録中の中間解析は行わないこととする。

なお、当初の想定より予後が良い場合には、サンプルサイズの上方修正や追跡期間の延長などの検討が必要となるため、6 か月以内に登録終了となることが予想される定期モニタリングのタイミングで、こうした修正が必要かどうかの検討を行う。

### 12.3.2. 中間解析の方法

中間解析は JCOG データセンターが行う。原則として中間解析中も登録は停止しない。

試験全体のαエラーを 5%に保つために、中間解析と最終解析における検定の多重性を Lan & DeMets の α 消費関数を用いて調整し、群間の生存期間の差について統計学的有意性を調べる。α 消費関数として、O'Brien & Fleming タイプを用いる 。

JCOG データセンターの当該グループ担当統計部門担当者は、必要に応じて中間解析時点までに解析計画書を作成する。実際の中間解析は、当該グループ担当ではない統計スタッフが行い、中間解析レポートを作成する。

それぞれの時期の解析において、治療法を共変量として含めた Cox 比例ハザードモデルによって、治療効果のハザード比及びその信頼区間を算出し、試験治療群(腹腔鏡下胃切除術)の全生存期間が標準治療群(開腹による胃切除術)のそれを上回り、多重性を調整したハザード比の信頼区間上限が許容ハザード比 1.54 を下回った場合、統計的に有意に非劣性が証明されたと判断する。また、非劣性の証明に引き続き多重性を調整したハザード比の信頼区間上限が 1 を下回った場合、統計的に有意に優越性が証明されたと判断する。

本試験の中間解析結果に基づく判断規準は以下のとおりである。

<u>1 回目(登録中)の中間解析</u>

- 標準治療群(開腹による胃切除術)に対して、試験治療群(腹腔鏡下胃切除術)の全生存期間での非劣性が示されなかった場合、あるいは、非劣性が証明されたものの優越性は証明されなかった場合はいずれの場合も試験を継続する。
- 標準治療群(開腹による胃切除術)に対して、試験治療群(腹腔鏡下胃切除術)の全生存期間での優越性が示された場合、試験を中止する(有効中止)。
- 試験治療群(腹腔鏡下胃切除術)の全生存曲線が標準治療群(開腹による胃切除術)のそれを下回っている場合には検定等の統計学的な判断に制約されずに総合的に試験中止の要否を検討することとするが、ハザード比の点推定値が許容ハザード域(ハザード比＞1.54)を超えて上回った場合(試験治療群(腹腔鏡下胃切除術)が許容範囲を超えて悪い場合)には、試験を中止する(無効中止)。

＜v1.2 での追記事項＞

- 全生存期間のイベント数が十分でないことから、無再発生存期間について、ハザード比の点推定値が許容ハザード域(ハザード比＞1.54)を超えて上回った場合{試験治療群(腹腔鏡下胃切除術)が許容範囲を超えて悪い場合}には、試験中止を検討する。

<u>2 回目(登録終了後)の中間解析</u>

- 標準治療群(開腹による胃切除術)に対して、試験治療群(腹腔鏡下胃切除術)の全生存期間での非劣性が示されなかった場合は試験を継続する。
- 標準治療群(開腹による胃切除術)に対して、試験治療群(腹腔鏡下胃切除術)の全生存期間での非劣性が示された場合、試験を中止する(有効中止)。
- 試験治療群(腹腔鏡下胃切除術)の全生存曲線が標準治療群(開腹による胃切除術)のそれを下回っている場合には検定等の統計学的な判断に制約されずに総合的に試験中止の要否を検討することとするが、ハザード比の点推定値が許容ハザード域(ハザード比＞1.54)を超えて上回った場合(試験治療群(腹腔鏡下胃切除術)が許容範囲を超えて悪い場合)には、試験を中止する(無効中止)。

中間解析時には以下の secondary endpoints の群間比較も行う。

<u>安全性の secondary endpoints:</u>

- 術後早期経過(排ガスまでの日数、鎮痛剤の使用割合、術後 3 日目まで及び入院期間中の体温の最高値)

<u>有効性の secondary endpoints:</u>

- 無再発生存期間

**○改訂箇所 2：適格規準の変更**

先行して、内視鏡的治療（EMR、ESD）が行われている場合の手術までの期間を、2 か月としておりましたが、他科からの紹介なども含めると、2 か月を超える場合もあります。内視鏡治療の対象となるような胃癌は予後良好ですので、手術までの期間がもう少し長くても予後に影響を与える可能性は極めて低いと考えられます。このため、期間について、再度検討を行い、先行して内視鏡的治療が行われている場合は治療後 3 か月（91 日）以内に、手術ということといたしました。適格規準、ならびに、プトロコール治療の規定に、その旨を追記いたしました。

二重取り消し線の削除、下線部の追加

**4.1 適格規準（組み入れ規準）**

4) 先行して EMR や ESD が行われている場合、EMR（ESD）後の病理組織学的検査により追加外科切除が必要と判断され※、以下の①～③をすべて満たす。

① 登録日が EMR（ESD）施行日から ~~56~~91 日以内である（EMR（ESD）後 ~~8~~13 週間後の同一曜日の登録は許容する）

② 先行する EMR（ESD）にて、穿孔がない。

③ EMR（ESD）後の内視鏡所見にて EMR（ESD）の切除縁が胃上部（U）にかからない。

下線部の追加

**6.1. プロトコール治療**

登録後 28 日以内にプロトコール治療を開始する。なお、EMR（ESD）施行例は EMR（ESD）施行日から 91 日以内にプロトコール治療を開始する。

**○改訂箇所 3：胃癌取扱い規約第 14 版ガイドライン第 3 版の記載追加**

プロトコール作成段階では、胃癌取扱い規約第 14 版および胃癌治療ガイドライン第 3 版は発効されておらず、胃癌学会にて配布されたドラフト案に沿って、記載していました。その後、胃癌取扱い規約第 14 版および胃癌治療ガイドラインが正式に出版され、ドラフト案段階では未固定であった術式の記載などが変更となりました。本試験でも、3 章への記載を追記することといたしました。

**3.4.2. 胃壁深達度（胃癌取扱い規約第 14 版）**

腫瘍の胃壁深達度は、以下のように定義される。

T0：癌がない
T1：癌の浸潤が粘膜（M）または粘膜下組織（SM）にとどまるもの
　T1a-M：癌の浸潤が粘膜にとどまるもの
　T1b-SM：癌の浸潤が粘膜下層にとどまるもの
T2-MP：癌の浸潤が粘膜下組織を超えているが、固有筋層（MP）にとどまるもの
T3-SS：癌の浸潤が粘膜下組織を超えているが、漿膜下組織（SS）にとどまるもの
T4：癌の浸潤が漿膜に近接または露出、あるいは他臓器に及ぶもの
　T4a-SE：癌の浸潤が漿膜表面に近接しているか、またはこれを破って遊離腹腔に露出しているもの（SE）
　T4b-SI：癌の浸潤が直接他臓器まで及ぶもの（SI）
TX：癌の浸潤の深さが不明なもの

**3.6. リンパ節郭清程度の分類（胃癌治療ガイドライン第 3 版）**

1) 胃全摘術
　D0　：D1 に満たない郭清
　D1　：No. 1～7
　D1+　：D1 ＋ No.8a、9、11p
　D2　：D1 ＋ No.8a、9、10、11、12a
　ただし食道浸潤癌では D1 に No.110 を、D2 には No.19、20、110、111 を追加する。
2) 幽門側胃切除術
　D0　：D1 に満たない郭清

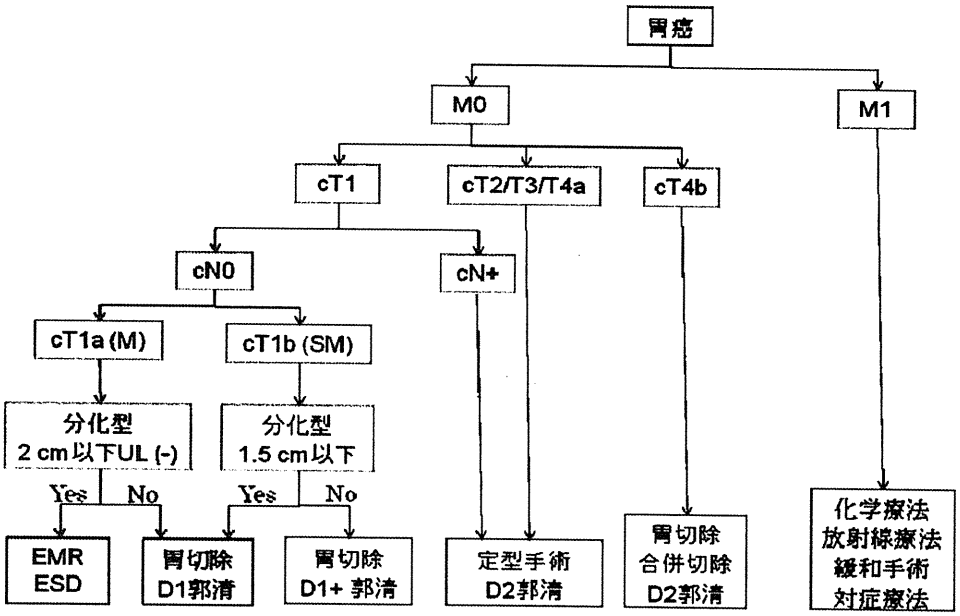
D1　　:No. 1、3、4sb、4d、5、6、7
D1+　　:D1 ＋ No.8a、9
D2　　:D1 ＋ No.8a、9、11p、12a

3) 幽門保存胃切除術
D0　　:D1 に満たない郭清
D1　　:No. 1、3、4sb、4d、6、7
D1+　　:D1 ＋ No.8a、9

4) 噴門側胃切除術
D0　　:D1 に満たない郭清
D1　　:No. 1、2、3a、4sa、4sb、7
D1+　　:D1 ＋ No.8a、9、11p

**○改訂箇所 4：リンパ節郭清の規定の追加**

胃癌治療ガイドライン 3 版では、cT1N0 には D1+または、D1 郭清が適応となります。




CRF レビューにより、登録例の大多数が cT1N0 として登録されているにもかかわらず、D2 郭清を実施している症例が多いことがわかりました。cT1N0 に対して、D2 を行った場合は「逸脱」となるのではないかとの指摘があり、グループ班会議にて検討いたしました。

その結果、術前・術中腫瘍深達度診断には限界があり、リンパ節転移がないことを肉眼で確認することはほぼ不可能であるため、cN1 とまではっきりと診断できないが、リンパ節転移が疑わしいような cT1N0 腫瘍では D2 郭清を行ってもよいことは胃癌治療ガイドラインにも書かれており、本試験でもそれに従うことでグループの合意が得られました。なお、胃癌治療ガイドラインにも今回の指摘を受け、より明確な補足説明が加えられる見通しです。この点に関して本文に追記し、郭清範囲の明確化を行うこととしました。

**6.1 プロトコール治療**

本試験におけるプロトコール治療とは、胃癌治療ガイドライン（医師用第 3 版）に則ったリンパ節郭清（D1, D1+~~No.8,9~~、または D2）を伴う腹腔鏡下あるいは開腹下での幽門側胃切除術（幽門保存胃切除を含む）を指す。

なお、胃癌治療ガイドライン（医師用第 3 版）では「原則として、cT1N0 腫瘍に対しては D1 または D1+郭清を行う。」と記載されているが、同時に「術前・術中の腫瘍深達度診断には限界があり、またリンパ節転移がないことを肉眼で確認することはほぼ不可能である。疑わしい場合は原則 D2 郭清を行う。」との記載がある。そのため、cN1 とは明確に診断できないが、転移が疑われるような cT1N0 腫瘍で D2 郭清を行うことは許容される。すなわち CRF に cT1N0 腫瘍と記載がある場合で D2 郭清を行っていてもプロトコール逸脱とはしない。

なんらかの理由で、手術日が登録後 29 日以降となった場合は、その理由を治療前報告用紙に記載すること。登録

後、手術日までに臨床検査値などが悪化した場合、手術を行うか中止するかは担当医の判断によるが、手術を行った場合には「治療前記録用紙」に、中止した場合には「治療終了報告用紙」に担当医の判断の詳細を記載すること。

**6.1.2. A 群:開腹胃切除術**

**2) 手術規定**

③リンパ節郭清及び主幹動脈の処理

胃癌治療ガイドライン(医師用第 3 版)に則ったリンパ節郭清(D1、D1+~~No.8a、9~~、または D2)を伴う幽門側胃切除術(幽門保存胃切除術を含む)を行う。郭清範囲に関する留意事項については「6.1.プロトコール治療」前文の記載を参照。

**6.1.3. B 群:腹腔鏡下胃切除術**

**3) 手術規定**

③リンパ節郭清及び主幹動脈の処理

胃癌治療ガイドライン(医師用第 3 版)に則ったリンパ節郭清(D1、D1+~~No.8a、9~~、または D2)を伴う腹腔鏡下幽門側胃切除術(幽門保存胃切除術を含む)を行う。幽門保存胃切除術の場合、幽門上リンパ節(#5)のリンパ節郭清を省略してもよい。また、腹腔神経を温存するために、左胃動脈の根部を温存して、左胃動脈幹リンパ節(#7)のリンパ節郭清を施行してもよい。郭清範囲に関する留意事項については「6.1.プロトコール治療」前文の記載を参照。

**○改訂箇所 5 : プロトコール治療中止規準の追加**

幽門側胃切除→胃全摘術に移行した場合にプロトコール治療中止とするかどうかについての取扱いの記載がありませんでした。現在、全摘を行った旨の報告はありませんが、6.2.プロトコール治療中止規準では、術中 Stage IV の場合しか規定されていないため、このような場合はプロトコール治療中止となる旨を追加いたしました。

**6.2.2.プロトコール治療中止の規準**

以下のいずれかの場合、プロトコール治療を中止する。

1)以下のいずれかにより、プロトコール治療無効と判断された場合

・術中所見にて、sStage IV と診断された場合

・胃全摘術に移行した場合

**○改訂箇所 6 : 有害事象項目の追加**

予期される有害事象に「創し開」を追加しました。

7.1.1.予期される有害反応・手術合併症

2) ④術後早期に一般的に予期される有害事象

創し開

**○改訂箇所 7 : 術者認定申請書の送付先の補完**

**6.1.1.手術担当責任医**

研究代表者は、以下の規準に従って、各参加施設の担当医の中から開腹手術、腹腔鏡下手術の手術担当責任医をそれぞれ指名する。

なお、術者認定申請者は IRB 承認書をデータセンターに送る前に、研究代表者(研究事務局)からの術者認定を受けること。術者認定申請者は、データセンターではなく、研究代表者へ連絡すること。

**○改訂箇所 8：研究者情報、定型記載の更新**

研究者情報を最新のものに更新し、JCOG プロトコールマニュアル（最新版）の記載内容をプロトコールに反映いたしました。主な変更箇所は 13 章、16 章となります。変更箇所はプロトコール本体に青字で示しております。

**○改訂箇所 9：IC 文書、グループ名・研究費名等の更新**

2011 年 4 月のグループ改編により「胃がんグループ」へと名称が変更になりました。本改訂に合わせ、IC 文書（QOL 調査あり、QOL 調査なしの両方のモデル説明同意文書）の記載を、下記のように更新いたしました。

| 変更前 | 変更後 |
|---|---|
| 胃がん外科グループ | 胃がんグループ |
| 13 この臨床試験の研究組織について<br>国内約 170 の医療機関が参加し、14 の専門分野別のグループで構成され、それぞれのグループが専門のがん研究を進めています。<br>• 厚生労働省がん研究助成金<br>「消化器悪性腫瘍に対する標準治療確立のための多施設共同研究」<br><br>この臨床試験は JCOG の中の「胃がん外科グループ」が主体となって行っています。この胃がん外科グループには、全国の 40 施設が参加しています。 | 国内約 180 の医療機関が参加し、15 の専門分野別のグループで構成され、それぞれのグループが専門のがん研究を進めています。<br>• 独立行政法人国立がん研究センター研究開発費「消化管悪性腫瘍に対する標準治療確立のための多施設共同研究」<br><br>この臨床試験は JCOG の中の「胃がんグループ」が主体となって行っています。この胃がんグループには、全国の 54 施設が参加しています。 |
| 19. 担当医の連絡先、研究代表者、研究事務局<br>片井（かたい） 均（ひとし）<br>国立がんセンター中央病院　胃外科 | <br>片井（かたい） 均（ひとし）<br>国立がん研究センター中央病院　胃外科 |

以上

# 研究成果の刊行に関する一覧表

別紙４

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 |
|---|---|---|---|---|---|
| Nonaka S, Katai H, et al. | Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway. | Gstric Cancer | 14(1) | 56-62 | 2011 |
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| | | | | | |
| | | | | | |

# 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

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

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**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

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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 $\chi^2$ test and Fisher's exact test (Statview; Abacus Concepts, Berkeley, CA, USA), and $P < 0.05$ was considered statistically significant.

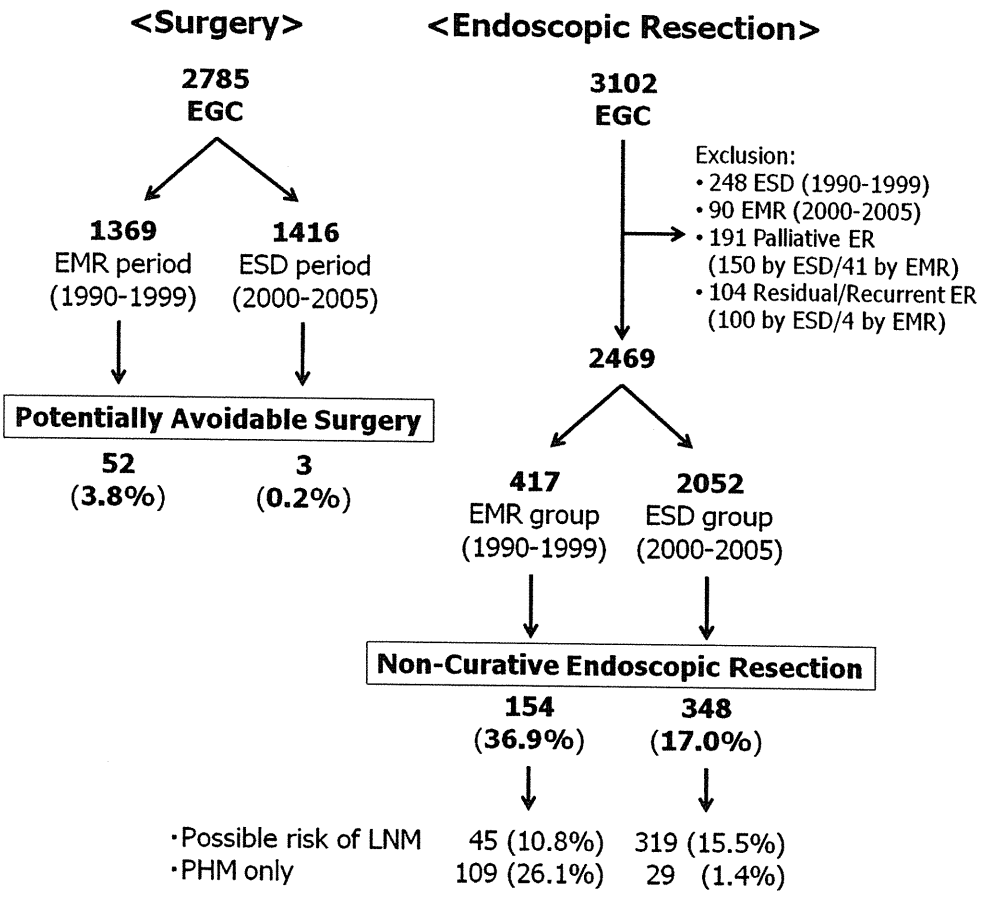


**Fig. 1** Outline of the study, including rates of potentially avoidable surgery and non-curative endoscopic resection based on the histological results. *EGC* Early gastric cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection, *LNM* lymph node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

**Table 3** Non-curative endoscopic resection

| |
|---|
| Non-curative with possible risk of lymph node metastasis |
| Submucosal deep invasion (sm2) |
| Positive lymphatic and/or venous invasion |
| Intramucosal cancer >30 mm in size with ulceration |
| Submucosal superficial invasion (sm1) >30 mm in size |
| Predominantly undifferentiated type adenocarcinoma |
| Positive vertical margin |
| Non-curative with positive or difficult to estimate horizontal margins only |

**Table 4** Rates of potentially avoidable surgery

| | EMR period (1990–1999) | ESD period (2000–2005) | *P* |
|---|---|---|---|
| Treated surgically | 1,369 | 1,416 | |
| Guideline lesion | 52 (3.8%) | 3 (0.2%) | <0.001 |
| Technical difficulty | 21 | 0 | <0.001 |
| Incorrect assessment | 31 | 3 | <0.001 |

*EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

## Results

### Potentially avoidable surgery

The study results are outlined in Fig. 1. 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 ($P < 0.001$) (Table 4). There were two possible contributory factors to potentially avoidable surgery: technical difficulty with ER and incorrect pre-therapeutic assessment of EGC. EMR was not possible in 21 patients where technical difficulty arose from there being a remnant stomach due to prior surgery; scarring from previous ulceration close to the lesion; and the location of the lesion, in particular those very close to the pylorus and the gastroesophageal junction. Thirty-one patients did not undergo EMR due to incorrect pre-therapeutic endoscopic findings suggesting submucosal invasion and unclear margins. In the ESD group, all attempted lesions were treated successfully with ESD, and, in the ESD period, there were three surgical patients with incorrect preoperative assessments with lesions thought to have submucosal invasion (Table 4).

### Non-curative ER with possible risk of lymph node metastasis and positive or difficult to estimate horizontal margins only

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 ($P < 0.001$) (Fig. 1) (Table 5). Reasons for non-curative ER are summarized in Table 6. The rates of sm2 invasion and positive lymphatic and/or venous involvement did not differ between the two groups. However, rates of intramucosal cancer more than 3 cm in size with ulceration, sm1 lesions more than 3 cm in size, and predominantly undifferentiated type adenocarcinoma in the ESD group significantly increased compared to those in the EMR group. The rate of positive vertical margins significantly decreased in the ESD group. In Table 6, we have listed the causes of non-curative endoscopic resection. Lesions considered non-curative with possible risk of lymph node metastasis may have been considered as such for one or a combination of overlapping criteria. To put this another way, the rate of non-curative ER with possible risk of lymph node metastasis regardless of horizontal margin increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ($P < 0.01$) (Table 5). Conversely, the rate of non-curative ER with positive or difficult to estimate horizontal margins only dramatically decreased in the ESD group (1.4%; 29/2,052)

**Table 5** Rates of non-curative endoscopic resection

| | EMR group % ($n = 417$) | ESD group % ($n = 2,052$) | *P* |
|---|---|---|---|
| Non-curative with possible LNM | 10.8 (45) | 15.5 (319) | <0.01 |
| Non-curative with PHM only | 26.1 (109) | 1.4 (29) | <0.001 |
| Total | 36.9 (154) | 17.0 (348) | <0.001 |

*EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin

**Table 6** Causes of non-curative endoscopic resection

| | EMR group % ($n = 417$) | ESD group % ($n = 2,052$) | *P* |
|---|---|---|---|
| sm2 cancer | 8.9 (37) | 7.5 (153) | NS |
| Positive lymphatic and/or venous invasion | 5.3 (22) | 5.4 (110) | NS |
| Intramucosal cancer >30 mm in size with ulceration | 0 (0) | 1.7 (34) | <0.004 |
| sm1 cancer >30 mm in size | 0 (0) | 2.3 (48) | <0.0003 |
| Predominantly undifferentiated type | 1.4 (6) | 3.8 (79) | <0.01 |
| Positive vertical margin | 4.6 (19) | 2.2 (46) | <0.007 |
| Positive horizontal margin | 31.4 (131) | 3.0 (62) | <0.001 |

In some patients there was more than one cause

*EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *sm2* submucosal deep invasion, *sm1* submucosal superficial invasion, *NS* not significant

compared to that in the EMR group (26.1%; 109/417) ($P < 0.001$) (Table 5).

### Complications

The rate of perforation in the EMR group (6.0%; 25/417) was significantly higher compared to that in the ESD group (3.0%; 62/2,052) ($P < 0.003$). All perforations were detected endoscopically during the procedure, except for one patient in the ESD group with a delayed perforation who had a gastric tube after esophagectomy. Seven patients in the EMR group and one patient in the ESD group underwent emergency surgery because the perforations were difficult to manage endoscopically using endoclips. Blood transfusion was required in one patient in each group.

## Discussion

This retrospective study shows that the rate of potentially avoidable surgery decreased significantly and the overall non-curative ER rate also decreased with the development of ESD. In the ESD group, the rate of non-curative endoscopically resected specimens with positive or difficult to estimate horizontal margins only significantly decreased compared with that in the EMR group, but the rate of non-curative ERs with possible risk of lymph node metastasis increased significantly.

The rate of potentially avoidable surgery was 3.8% (52/1,369) during the EMR period and 0.2% (3/1,416) during the ESD period ($P < 0.001$) (Table 4). We believe this may be as a result of two factors, the technical progress of ER and improved diagnostic accuracy. The progress of ER with EMR, and now ESD, over the past two decades has involved major breakthroughs in endoscopy and has revolutionized the treatment of EGC. The advent of ESD has enabled us to achieve a higher rate of en-bloc resection in situations not possible before. These include remnant stomachs, scarring from previous gastric ulceration, and certain technically difficult locations. Despite the recent development of new technology such as narrow band and autofluorescence imaging [32, 33], there have been no significant changes in our ability to diagnose the depth of invasion of EGC [27, 28]. Other studies have reported that the endoscopic staging of EGC is not always accurate and is correct in only 80–90% of cases, even with endoscopic ultrasonography [26, 34–36]. In our study, we found that incorrect preoperative assessments such as endoscopic overstaging leading to potentially avoidable surgery dropped significantly with the use of ESD (Table 4), but we believe that the increased use of ESD for enhanced diagnosis, rather than improvements in other diagnostic modalities, resulted in this reduction.

For reference, the rate of surgery for lesions included within the National Cancer Center expanded criteria was 4.7% (67/1,416) during the ESD period (data not shown). These lesions consisted of 18 intramucosal cancers >20 mm without ulceration, 33 intramucosal cancers ≤30 mm in size with ulceration, and 16 sm1 cancers ≤30 mm in size. It is believed that surgery on some of these lesions was potentially avoidable, but a direct comparison using the guideline criteria of the Japanese Gastric Cancer Association and the National Cancer Center expanded criteria cannot be made because of differences between the two sets of criteria.

The rate of non-curative ER, secondary to positive or difficult to estimate horizontal margins only, in the ESD group (1.4%; 29/2,052) significantly decreased compared to that in the EMR group (26.1%; 109/417) ($P < 0.001$) (Table 5). This reflects the inability of EMR to resect large lesions en bloc, the lesion often being resected in multiple fragments, making it difficult to ensure complete resection [9–11]. The other main problem that arises with performing EMR, even for small lesions, is the uncertainty regarding inaccurate resection margins. Several previous articles have reported higher rates of local recurrence caused by piecemeal resection and positive tumor margins [12, 13, 22, 23, 37]. The development of ESD has addressed these problems, as it enables an en-bloc resection with tumor-free margins.

On the other hand, the rate of non-curative ERs with possible risk of lymph node metastasis (which should ideally be managed by gastrectomy with lymph node dissection) increased in the ESD group (15.5%:319/2,052) compared to that in the EMR group (10.8%:45/417) ($P < 0.01$) (Table 5). This five percent difference could have occurred due to several reasons, but the primary cause was most likely the increase in the number of patients who underwent diagnostic ESD for borderline lesions which were either difficult to resect technically by EMR or difficult to estimate tumor depth accurately. Specifically, the introduction of the National Cancer Center expanded criteria and the ability of ESD to resect larger lesions are two possible reasons for the increase in the number of intramucosal cancers more than 3 cm in size with ulceration and sm1 lesions more than 3 cm in size for which ER was undertaken. An increase in the number of lesions with predominantly undifferentiated adenocarcinoma also occurred, most likely because the heterogeneity of gastric carcinoma may increase in larger-size lesions. Thus, this five percent rise in the rate of non-curative ERs with possible risk of lymph node metastasis has to be weighed against the potential advantages in undertaking ESD and the significantly reduced rate of potentially avoidable surgery. Oda et al. [31] reported that the actual rate of lymph node metastases, as determined from surgically resected

specimens, in a group of cases of 'non-curative ESD with possible risk of lymph node metastasis', was 6.3%. This emphasizes the fact that this cohort of patients should receive additional surgery.

In the present study, the rate of perforation in the EMR group (6.0%) was significantly higher compared to that in the ESD group (3.0%) although it is widely recognized that the rate of perforation with ESD is higher than that with EMR [22]. There is no evident explanation for this result, but one possible reason may be that EMR procedures were performed more aggressively because of curative intent in the EMR group.

The surgically resected stomach never returns to its natural state. Currently, the pathway whereby we use ESD as the optimal therapeutic strategy for the treatment of EGC seems to reduce the rate of potentially avoidable surgery and allows us to more appropriately select those cases that would benefit from additional surgery, as it enables more accurate histological assessment, particularly in difficult EGC cases. As a result, this pathway has brought about major benefits for patients by reducing potentially avoidable surgery, because with this strategy the final diagnosis is obtained with higher reliability due to precise feedback from histological assessments. However, it would be prudent to advise caution in performing ESD for EGC unless the indications have been carefully reviewed in the individual to ensure that the EGC is within the established selection criteria. We would emphasize that recognition of resectability and curability are two very different matters. It is also important to recognize the role of ESD in providing enhanced diagnostic information, thus contributing to the optimal therapy being undertaken for the appropriate indication.

### Limitations

This study was retrospective and there were differences in criteria for ER between the two groups. In addition, the transitional phase was at the turn of the twenty-first century, but it was not clearly delineated as both procedures were being used at that time. However, we believe that by analysis by procedure (EMR and ESD) we have minimized the impact of this last factor.

## Conclusions

We believe that a pathway of undertaking ESD in lesions where it may be difficult to estimate the depth of invasion and in technically difficult cases results in a significant decrease in the rate of potentially avoidable surgery, this being due to the advantages associated with not only a potentially curative procedure, but also one which provides enhanced diagnostic information and consequently enables more appropriate therapy.

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**Conflict of interest** None.

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# Present and Future Status of Gastric Cancer Surgery

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The type of surgery and the role of adjuvant therapies in the treatment of gastric cancer have changed in recent times. The treatment of gastric cancer with curative intent is moving away from standard D2 or more extensive surgery to a tailored approach depending on the stage of the disease. Data collected from extensive lymphadenectomy for all stages of gastric cancer have confirmed that some subsets of early gastric cancer are very low risk for nodal metastasis. This group of patients may benefit from resection by endoscopic or laparoscopic techniques and may also be suitable for function-preserving procedures. The extent of resection for gastric cancer has always excited debate. D2 gastrectomy was criticized for its higher mortality in the early European Phase III trials, but recent studies from Taiwan and Italy have shown that the procedure is safe when performed by experienced surgeons and has a survival benefit over D1 gastrectomy. The role of para-aortic lymph node dissection for nodes without apparent metastasis in advanced gastric cancer was assessed by a Phase III Japanese trial and showed no additional benefit over D2 resection. Radical gastric resections, involving resection of adjacent organs for direct tumor invasion result in higher rates of complications, and the role of multi-visceral resections has also been reevaluated. Effective adjuvant therapies for gastric cancer have been reported since the early part of 2000. Development of more effective adjuvant therapy combined with D2 resection should continue to improve survival in the future.

*Key words: gastric cancer – surgery – function-preserving gastrectomy – laparoscopic gastrectomy – adjuvant therapy*

## INTRODUCTION

Chemotherapy helps to prolong survival in cases of advanced disease, but surgery is still the mainstay of curative treatment for gastric cancer. From uniform use of D2 or more extensive surgery, surgical treatment has evolved to become more tailor-made depending on the stage of the disease.

Extensive operations have been reevaluated for advanced gastric cancer and the role of effective adjuvant therapies in this setting has expanded. More radical operations than D2 for gastric cancer have often been carried out without clear evidence until clinical trials have failed to show the survival benefit of these procedures over D2. For early gastric cancer, less extensive resections and minimally invasive techniques have been developed, such as function-preserving procedures and laparoscopic surgery.

## D2 LYMPHADENECTOMY

Total or subtotal gastrectomy with D2 lymphadenectomy is the gold standard surgical treatment for gastric cancer in eastern Asia. The procedure initially developed in Japan, has been safely performed and provided good survival outcomes for patients with gastric cancer regardless of disease stage (1,2). The use of this technique has been challenged by Western clinical trials since the 1990s.