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| 4601201 | 鹿児島大学医学部第１外科 | 愛甲 孝 | 帆北 修一 |

### 16.7. JCOG 臨床試験審査委員会ならびに効果・安全性評価委員会

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## 17. 研究結果の発表

本試験終了後、研究代表者は速やかにその結果をまとめ、参加者の了解の後しかるべき英文誌および学会に発表する。全研究協力者は List of authors として論文に掲載する。

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## 19. 付表

・胃癌取扱い規約リンパ節分類および群分類
・説明文書・同意書
・ヘルシンキ宣言（和訳）
・ケースレポートフォームドラフト

付表 1

胃癌取扱い規約第 13 版におけるリンパ節の番号と名称

| | |
|---|---|
| No.1 | 右噴門リンパ節 |
| No.2 | 左噴門リンパ節 |
| No.3 | 小彎リンパ節 |
| No.4sa | 大彎リンパ節左群（短胃動脈） |
| No.4sb | 大彎リンパ節左群（左胃大網動脈に沿う） |
| No.4d | 大彎リンパ節右群（右胃大網動脈に沿う） |
| No.5 | 幽門上リンパ節 |
| No.6 | 幽門下リンパ節 |
| No.7 | 左胃動脈幹リンパ節 |
| No.8a | 総肝動脈前上部リンパ節 |
| No.8p | 総肝動脈後部リンパ節 |
| No.9 | 腹腔動脈周囲リンパ節 |
| No.10 | 脾門リンパ節 |
| No.11p | 脾動脈幹近位リンパ節 |
| No.11d | 脾動脈幹遠位リンパ節 |
| No.12a | 肝十二指腸間膜内リンパ節（肝動脈に沿う） |
| No.12b | 肝十二指腸間膜内リンパ節（胆管に沿う） |
| No.12p | 肝十二指腸間膜内リンパ節（門脈に沿う） |
| No.13 | 膵頭後部リンパ節 |
| No.14v | 上腸間膜静脈に沿うリンパ節 |
| No.14a | 上腸間膜動脈に沿うリンパ節 |
| No.15 | 中結腸動脈周囲リンパ節 |
| No.16a1 | 腹部大動脈周囲リンパ節 a1 |
| No.16a2 | 腹部大動脈周囲リンパ節 a2 |
| No.16b1 | 腹部大動脈周囲リンパ節 b1 |
| No.16b2 | 腹部大動脈周囲リンパ節 b2 |
| No.17 | 膵頭前部リンパ節 |
| No.18 | 下膵リンパ節 |
| No.19 | 横隔下リンパ節 |
| No.20 | 食道裂孔部リンパ節 |
| No.110 | 胸部下部食道リンパ節 |
| No.111 | 横隔上リンパ節 |
| No.112 | 後縦隔リンパ節 |

付表２

原発巣の占居部位によるリンパ節群別一覧表（胃癌取扱い規約第 13 版）

| 占居部位<br>リンパ節 No. | LMU/MUL<br>MLU/UML | LD/L | LM/M/ML | MU/UM | U | E+ |
|---|---|---|---|---|---|---|
| 1 | 1 | 2 | 1 | 1 | 1 | |
| 2 | 1 | M | 3 | 1 | 1 | |
| 3 | 1 | 1 | 1 | 1 | 1 | |
| 4sa | 1 | M | 3 | 1 | 1 | |
| 4sb | 1 | 3 | 1 | 1 | 1 | |
| 4d | 1 | 1 | 1 | 1 | 2 | |
| 5 | 1 | 1 | 1 | 1 | 3 | |
| 6 | 1 | 1 | 1 | 1 | 3 | |
| 7 | 2 | 2 | 2 | 2 | 2 | |
| 8a | 2 | 2 | 2 | 2 | 2 | |
| 8p | 3 | 3 | 3 | 3 | 3 | |
| 9 | 2 | 2 | 2 | 2 | 2 | |
| 10 | 2 | M | 3 | 2 | 2 | |
| 11p | 2 | 2 | 2 | 2 | 2 | |
| 11d | 2 | M | 3 | 2 | 2 | |
| 12a | 2 | 2 | 2 | 2 | 3 | |
| 12b/p | 3 | 3 | 3 | 3 | 3 | |
| 13 | 3 | 3 | 3 | M | M | |
| 14a | M | M | M | M | M | |
| 14v | 2 | 2 | 3 | 3 | M | |
| 15 | M | M | M | M | M | |
| 16a2/16b1 | 3 | 3 | 3 | 3 | 3 | |
| 16a1/16b2 | M | M | M | M | M | M |
| 17 | M | M | M | M | M | M |
| 18 | M | M | M | M | M | M |
| 19 | 3 | M | M | 3 | 3 | 2 |
| 20 | 3 | M | M | 3 | 3 | 1 |
| 110 | M | M | M | M | M | 3 |
| 111 | M | M | M | M | M | 3 |
| 112 | M | M | M | M | M | 3 |

E+:食道に浸潤する癌　　群分類の「M」は遠隔転

# 説明同意文書

**研究名：JCOG 0110-MF「上部進行胃癌に対する胃全摘術における脾合併切除の意義に関するランダム化比較試験」**

1) あなたの病状

担当医から説明がありましたように、あなたの胃にがんができています。あなたの胃がんは進行がんと考えられており、胃の入り口に近い部位に生じていて、完全に切除するためには胃を全部摘出すること（胃全摘）が必要です。ただし肝臓や遠くのリンパ節への転移は見つかっておらず、手術で根治が望める状態であると考えられています。胃がん手術後の予後は、がんの深さ、リンパ節転移の程度、腹膜や肝臓などへの転移の有無によって決まります。胃がんの進行程度を表すステージ（病期）は、ステージ1A、1B、2、3A、3B、4の6段階ありますが、これまでの検査の結果、あなたの胃がんはステージ1Bから4までの範囲にあると考えられ、予想される5年生存率も20%から90%と幅があります。最終的なステージは手術後の病理検索の結果で決まります。

2) 胃がんとリンパ節転移、リンパ節郭清、予後

胃がんはリンパ節に転移しやすいがんです。リンパ節転移が進むと、全身にがん細胞が広がります。早期胃がんでも約10%、進行がんでは50%以上の確率でリンパ節転移が認められます。胃がんのリンパ節転移は、胃のすぐそばのリンパ節（第1群リンパ節）に生じて徐々に離れた部位（第2群、3群リンパ節）へと広がりますので、たとえ転移があってもこれを遠くから包み込むようにして十分に切除することにより、治癒する可能性が得られます。リンパ節に転移があるかどうかは手術中には正確に判断できず、摘出したリンパ節を術後に顕微鏡で検査して初めて転移の有無が判明します。リンパ節の切除（郭清（かくせい）といいます）は、胃がんの手術において重要な部分を占めており、通常、第2群までのリンパ節が郭清されます。

3) 上部胃がんと脾臓

胃がんでは、がんが胃のどの位置にあるかによって、転移しやすいリンパ節の場所が変わります。「第2群リンパ節」といっても、胃の上部のがんと下部のがんでは範囲が異なるのです。胃の左背側には脾臓という握りこぶしくらいの大きさの臓器がありますが、胃上部のがんの場合、この脾臓のすぐそば（脾門部）のリンパ節にも転移することがあり、この脾門リンパ節も第2群に含まれています。したがって、胃上部の進行胃がんに対しては、胃と同時に脾臓も合併切除することが行われてきています。

4) 脾臓の役割

脾臓は、古くなった血小板などの血液成分を壊す働きがあります。また、体の免疫の調整に関しても一役を担っています。脾臓を摘出（脾摘）すると、一時的に血液中の血小板の数が増加しますが、やがて骨髄が代役を果たすようになりますので数ヶ月で血小板数は元に戻ります。また、免疫力が低下することがあり、肺炎球菌などの感染が起こりやすく

なるとされています。脾臓はまた、腫瘍に対する生体の免疫に関与するという研究がありますが、脾臓を摘出することが腫瘍の増殖とどう関係するかは、明確にされていません。

5) 胃全摘と脾摘

胃上部の進行がんでは胃全摘とともに脾摘も行われると述べましたが、実は脾臓を同時に摘出することの意義はきちんと証明されているわけではありません。脾門部のリンパ節に転移があった場合、脾摘を行うとこの転移を切除することができますが、一方で、脾摘操作により術中の出血量が増え、術後の合併症（脾臓のそばにある膵臓からの膵液の漏れや、腹腔内の感染）が生じやすくなったり、脾臓を失うことにより体の免疫力が低下して肺炎球菌という細菌の感染症が増えたりする可能性もあります。西洋諸国では、脾摘により術後の合併症率や手術死亡率が明らかに高くなるため、近年これを極力避けようという考えが支配的になっています。しかしわが国では、術後合併症は増えても手術死亡率が高くなるという事実はなく、むしろ転移リンパ節を切除する意義が注目されています。

これまでに胃上部進行がんで脾摘を行った記録を検討すると、約 15～20%の患者さんで脾門リンパ節に転移が見られ、その転移のある患者さんの 20～25%が 5 年以上生存しています。つまり脾摘をしたから助かった、と考えられる患者さんがいます。ところが一方、脾摘をした患者さん全体としなかった患者さん全体を比べると、脾摘をしなかった患者さんの生存率の方が高いという結果も出ています。ただしこれは、より進行したがんの場合ほど脾摘が行われることが多いため、脾摘患者さんの生存率が低く出てしまうとも解釈されています。

6) この臨床試験について

このように、胃上部の進行がんに対して胃全摘を行う場合に、同時に脾摘を行うことが生存の可能性を高めるかどうかは分かっていません。これまでにも多くの学会で論じられてきましたが結論は出ていません。

この問題に科学的な結論を下すためには、きちんと計画された臨床試験が必須となります。本臨床試験は、がんの専門病院を中心に構成される日本臨床腫瘍研究グループ（JCOG）の胃がん外科チームが厚生労働省の研究費を得て計画したもので、同じような病態の多数の患者さんに、脾摘を行うグループと行わないグループに分かれていただき、長期間経過を追って、どちらが優れた術式かを決めようというものです。この臨床試験で得られた結果は、将来、多くの胃がん患者さんが胃全摘を受ける際に、脾摘が行われるかどうかを決定する大変重要な根拠となるはずです。

7) この臨床試験の実際の手順

あなたがこの臨床試験への参加に同意されたとしましょう。手術が始まり、通常の手順で腹腔内が検索されます。腹膜転移や肝転移がないことが確認され、腹膜洗浄細胞診も行われます。大動脈周囲などの胃から離れた部位のリンパ節に転移がないこと、さらに脾門部にも明らかに腫脹したリンパ節はないことが確認されます。胃全摘を行えばがんは取り切れそうだ、という段階にきました。ここまで確認して初めて、臨床試験に登録するかど

うか決定されます。以上のうちどれか一つでも当てはまらない場合は、臨床試験には入らずに、担当医が最良と考える治療が行われます。

臨床試験に登録されると、胃全摘に加えて脾摘を行うかどうかが決定されることになります。二つのグループで患者さんの特徴に偏りが生じないよう、病院とは独立した JCOG のデータセンターが、ランダム割付けと呼ばれる方法で決定します。この結果にしたがって手術が行われます。あなたは手術後に、担当医から脾摘が行われたかどうかを知らされますが、その後の治療や経過観察は脾摘の有無にかかわらずまったく同じように行われます。この臨床試験には、合計 500 人の患者さんの登録を予定しています。

進行胃がんの手術後に、再発を予防したいという考えから抗がん剤が使われることがあります。しかしこれまでの多くの臨床試験でも、手術でがんが取りきれたと考えられる場合に抗がん剤を使うこと（補助化学療法といいます）で再発が予防されるという結論は得られていません。本臨床試験では、補助化学療法を行わずに経過を観察することになります。不幸にも再発が判明した時は、抗がん剤をはじめとするあらゆる手段で対処します。もしあなたが初めから補助化学療法を希望される場合はこの臨床試験には参加できませんので、担当医にお知らせください。

8)　その他の治療法について

あなたの胃がんを治療するには、内視鏡的切除では不十分で、手術が必要です。また、抗がん剤や放射線療法だけでは治癒は望めません。手術方法としては、ご説明しました胃全摘術の他に、胃の下部を残す噴門側胃切除術という方法があります。ただし、あなたの胃がんでは十分な範囲の胃とリンパ節を切除する必要があるため、たとえ胃の下部を残しても十分な機能は望めず、むしろ食べ物の流れが悪くなる場合もありますので、胃全摘が望ましいと考えられています。リンパ節の郭清範囲では、ご説明しました第 2 群までの郭清が現在標準的に行われていますが、さらに遠くの第 3 群までの郭清も技術的には可能です。ただし第 3 群までの郭清が胃がんの治癒に貢献するかどうかは分かっておらず、現在臨床試験が進められています。

9)　この臨床試験に参加することの利益と不利益

この臨床試験に参加することで、医療費の免除などの直接的な利益は得られません。もちろん従来から行われている手術ですので、経済的負担が増えるということもありません。

臨床試験に登録されるかどうかは、手術中に腹腔内を十分検索してから決定されますので、この試験に同意したからといって無理やり無用な手術が行われるということもありません。脾摘を行うことも行わないことも、外科医には十分に慣れた手順ですから、新しい種類の合併症が生じるということもありません。

この臨床試験では術後 5 年間にわたる経過追跡の内容が詳細に規定されていますので、試験に参加しない場合よりも細かいフォローアップが行われることになるでしょう（そのために若干医療費が増える可能性があります）。

10)　この臨床試験への参加に同意されなかった場合、および同意の撤回

この臨床試験への参加に同意されなかった場合でも、あなたはいかなる不利益も受けることはありません。また一旦同意しても、いつでもこれを撤回することができます。

11) 人権およびプライバシーの保護、データの二次利用

この臨床試験に参加した場合、あなたのお名前や個人情報は厳重に保護されます。データセンターのデータベースにも、あなたのお名前は登録されません。

この試験が適正かつ安全に実施され、患者さんの人権が守られており、かつ検査や診断の結果が正しく報告されていることを確認する目的で、JCOG 委員会の指名する他の医療機関や研究機関の研究者（医師など）が、あなたのカルテや検査記録を直接見にくる調査を行うことがあります。この場合もあなたの個人的情報は厳重に守られ、外部に漏れることはありません。

また、JCOG 委員会が承認した場合に限り、あなたの個人識別情報とリンクしない形でデータを二次利用する可能性があります（本臨床試験と同様の目的で行われた他の試験と、総合的に解析する場合、など)。この場合もあなたの個人的情報は厳重に守られます。

12) 質問の自由

この臨床試験の内容や治療の内容について、ご不明な点がありましたらご質問ください。

この臨床試験の当院における研究責任者、担当医は、

＊＊＊＊　です。(各施設で記入)

この臨床試験の研究代表者および研究事務局は以下の通りです。

研究代表者：笹子　充、研究事務局：佐野　武

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# 同　意　書

＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院長　殿

カルテ番号　＿＿＿＿＿＿＿＿

患者氏名　＿＿＿＿＿＿＿＿

臨床研究名：JCOG 0110-MF「上部進行胃癌に対する胃全摘術における脾合併切除の意義に関するランダム化比較試験」

説明内容：

- □ 病名、病状、予後
- □ 本研究が臨床試験であること。厚生省研究助成金に基づく公的研究であること。
- □ 試験の背景、目的、意義
- □ 治療の内容
- □ 治療法がランダム割付されること
- □ 治療により期待される効果と予測される副作用
- □ 費用が保険制度に従った自己負担であること
- □ 本試験に参加しなかった場合に受けられる他の治療法
- □ 試験参加に伴って生じる利益と不利益
- □ 試験に参加しない場合でも不利益を受けないこと
- □ 試験への参加に同意した後でも随時これを撤回できること
- □ 第三者による病歴の直接閲覧の可能性、データ二次利用の可能性
- □ プライバシーは守られること
- □ 現状に応じた変更の可能性（緊急の場合等の医学的処置）
- □ 質問の自由

上記の臨床試験について、担当医から説明を受けよく理解しましたので、試験に参加します。

患者本人署名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

署名年月日　：　平成　　年　　月　　日

私は、今回の試験について上記の項目を説明し、同意が得られたことを認めます。

担当医署名　：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

説明年月日　：　平成　　年　　月　　日

署名年月日　：　平成　　年　　月　　日

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# Gastric Cancer Surgery: Morbidity and Mortality Results From a Prospective Randomized Controlled Trial Comparing D2 and Extended Para-Aortic Lymphadenectomy—Japan Clinical Oncology Group Study 9501

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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## ABSTRACT

**Purpose**
Radical gastrectomy with regional lymphadenectomy is the only curative treatment option for gastric cancer. The extent of lymphadenectomy, however, is controversial. The two European randomized trials only reported an increase in operative morbidity and mortality, but failed to show survival benefit, in the D2 lymphadenectomy group. We conducted a randomized controlled trial to compare the Japanese standard D2 and D2 + para-aortic nodal dissection.

**Patients and Methods**
Only experienced surgeons in both procedures from 24 Japanese institutions participated in the study. Patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) who were surgically fit were intraoperatively randomized. Postoperative morbidity and hospital mortality were recorded prospectively in a fixed format and were compared between the two groups in this study.

**Results**
A total of 523 patients were randomized between July 1995 and April 2001. Postoperative complications were reported in 24.5% of all patients. Although the morbidity for the extended surgery group (28.1%) was slightly higher than the standard group (20.9%), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the two groups. Hospital mortality was reported at 0.80%: one patient in each group died of operative complications, while one from each group died of rapid progressive cancer while inpatient.

**Conclusion**
Specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Para-aortic lymphadenectomy could be added without increasing major surgical complications in this setting.

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## INTRODUCTION

Gastric cancer is the second most common malignancy in the world, and surgical resection remains the only curative treatment option. Lymph node metastases occur during the early stages of this disease, and regional lymphadenectomy is recommended as part of radical gastrectomy. However, the extent of lymphadenectomy to achieve the optimal result is controversial, and there is no worldwide consensus.

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s.[1] This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches). Early studies have reported that between 30% to 40% of patients

**Table 1.** Eligibility Criteria of the Study

| |
|---|
| Before operation |
| Entry criteria |
| Histologically proven adenocarcinoma |
| 75 years or younger |
| Forced expiratory volume in 1 second ≥ 50% |
| Arterial oxygen pressure in room air ≥ 70 mm Hg |
| Creatinine clearance ≥ 50 mL/min |
| Written consent |
| Exclusion criteria |
| Carcinoma in the remnant stomach |
| Borrmann type 4 (linitis plastica) |
| Synchronous or metachronous malignancy in other organs except for cervical carcinoma in situ and colorectal focal cancer in adenoma |
| Past history of myocardial infarction or positive results of exercise ECG |
| Liver cirrhosis or chronic liver disease with indocyanine green test ≥ 10% |
| During operation |
| Macroscopic T staging is T2-subserosa, T3, or T4 |
| Potentially curative operation is possible |
| No gross metastasis in para-aortic nodes (frozen section diagnosis not allowed) |
| Peritoneal lavage cytology is negative for cancer cells |

with positive lymph node metastases including the second tier lymph nodes, have survived longer than 5 years with D2 lymphadenectomy.[2] However, D2 gastrectomy has a steep learning curve,[3] and may be associated with a higher-than-expected operative morbidity and mortality.

Two European randomized controlled trials comparing D1 and D2 gastrectomy revealed a high operative mortality exceeding 10% in the D2 group.[4,5] Based on these reports, the British National Health Service Cancer Guidance discourages the use of D2 technique in routine clinical practice.[6] In contrast, D2 gastrectomy is considered a standard and safe procedure in Japan, where 100,000 cases of gastric cancers are diagnosed every year. General surgeons are taught this technique early during their surgical training.[7] The Japanese nationwide registry reported an operative mortality of less than 2%, and in specialized institutions, less than 1% for D2 gastrectomy.[8,9]

Since the eighties, even more radical extended lymphadenectomy procedures had been practiced in many Japanese specialized centers. It was reported that 20% to 30% of patients with nonearly gastric cancer had microscopic metastasis present in the para-aortic nodes.[10-13] The 5-year survival for these patients has reached 14% to 30% after extended systematic dissection. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected, primarily for ultimate local tumor control. However, this extended dissection may not only increase operative morbidity but also may effect the function of other abdominal organs.

There has never been a prospective study to assess the perioperative morbidity and mortality in Japanese patients after D2 gastrectomy or more extended surgery. To evaluate the survival benefit and operative complications of D2 gastrectomy and extended para-aortic dissection in gastric cancer surgery, a multi-institutional randomized controlled trial was conducted on behalf of the Japan Clinical Oncology Group (JCOG). The accrual closed with 523 patients. We hereby present the data on the operative morbidity and mortality, which are the secondary end points of this trial. Survival analysis is scheduled to take place in August 2006.

## PATIENTS AND METHODS

### *Objectives and End Points of the Study*

A prospective randomized controlled trial was designed to compare the two surgical techniques: the standard lymphadenectomy and the standard lymphadenectomy with the addition of para-aortic node dissection for gastric cancer. Only surgeons with sufficient experience of para-aortic dissection for gastric cancer participated in the trial. Since the role of neoadjuvant and adjuvant chemotherapy was not established, no patients received chemotherapy until recurrent disease was diagnosed.

The primary end point was the overall survival, while the secondary end points were the relapse-free survival, operative morbidity, hospital mortality, and quality of life. Randomization and data handling for this study was performed by the Data Centre of the JCOG, a government-sponsored organization for multi-institutional clinical trials.[14]

### *Eligibility Criteria*

Eligibility criteria for this study are shown in Table 1. Patients with advanced gastric cancer deemed curable and fit for surgery were recruited into the trial following informed consent. Borrmann type 4 tumors (linitis plastica) were excluded because of their very poor prognosis after surgery. Liver cirrhosis and ischemic heart disease were important risk factors for mortality after surgery and hence were excluded from the study. Para-aortic lymph node metastasis is extremely rare in T1 (invasion confined

to the mucosa or submucosa) and T2-MP tumors (invasion confined to the muscularis propria); hence, these patients were not eligible for randomization. Only patients diagnosed with T2-SS (subserosal invasion) or deeper tumors at the time of laparotomy were included in the study. T2-SS is clinically recognized as a white discoloration on the serosal surface, without overt tumor serosal exposure.

During the operation, the para-aortic nodes were inspected to exclude patients with gross metastasis (enlarged and/or hard nodes) in this region. Frozen section diagnosis of the para-aortic nodes was forbidden to avoid technical contamination between the two groups of patients. Peritoneal lavage cytology was performed immediately after initial laparotomy, and absence of free cancer cells was confirmed before enrollment.

### Random Assignment

While waiting for the result of lavage cytology, the surgeon examined the above eligibility criteria and started the D2 procedure. When the negative cytology result was obtained 30 to 60 minutes later, he informed the JCOG Data Centre for enrollment. Patients were then randomly assigned either to receive standard lymphadenectomy (group A) or extended lymphadenectomy (group B). The sizes of the groups were balanced according to T stage (T2 *v* T3/T4), tumor growth pattern (expansive *v* infiltrative growth), and institution. The randomization arm was notified to the surgeon immediately, who then completed the operation according to the allocated protocol.

### Surgical Methods

*Group A: Standard D2 gastrectomy.* Patients were treated with gastrectomy and D2 lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total, proximal subtotal, or distal subtotal gastrectomy. D2 lymphadenectomy was a standard procedure for dissection of tumors located in the upper two thirds of the stomach as defined in the 12th edition of the Japanese Classification (1993)[15] when the study was initially designed. An extended D2 lymphadenectomy was performed for tumors located in the lower third of the stomach, which involves further dissecting the hepatoduodenal nodes (No.12a), retropancreatic nodes (No.13) and nodes along the superior mesenteric vein (No.14v). This technique was frequently performed as a standard procedure in the specialized centers, and thus adopted in this study (all except No.13 have been integrated as "D2" in the 13th edition of Japanese classification[16]).

In total or proximal subtotal gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy, while it was preserved in distal subtotal gastrectomy for distal tumors.

*Group B: D2 gastrectomy combined with para-aortic lymphadenectomy.* Patients in this group had similar procedure to group A, but with additional para-aortic lymph node dissection. The area to be dissected was defined in the Japanese classification (Fig 1). Proximal tumors were treated with the standard D2 lymphadenectomy, and also all "No.16-a2" (para-aortic nodes between the level of the celiac axis and the left renal vein) and "No.16-b1" (para-aortic nodes between the left renal vein and the inferior mesenteric artery) were removed. Standard distal subtotal gastrectomy was performed for the distal tumors including the "No.16-a2" and "No.16-b1" nodes; however, dissection of the left upper lateral nodes ("No.16-a2-lat") was optional.

Both group A and group B patients were followed up according to a fixed schedule, without receiving adjuvant chemotherapy.

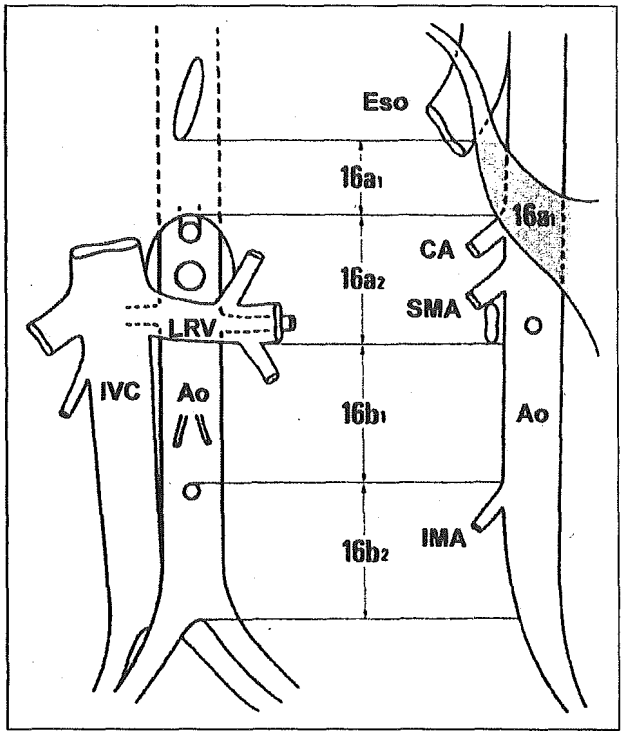


**Fig 1.** Anatomic definitions of para-aortic lymph nodes.[15] The nodes No.16a2 and No.16b1 are defined as "regional nodes" and were dissected in the extended surgery group. Ao, aorta; CA, celiac artery; Eso, esophagus; IMA, inferior mesenteric artery; IVC, inferior vena cava; LRV, left renal vein; SMA, superior mesenteric artery.

### Evaluation of Operative Morbidity and Mortality

Operative methods and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma.[15] The following information was included on the case report form for prospective data collection concerning the four major groups of operative morbidity: presence or absence of anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia. Anastomotic leak was diagnosed radiologically either on routine postoperative contrast swallow or based on clinical suspicion, and was recorded regardless of its clinical significance. Pancreatic fistula was usually diagnosed when fluid with a high amylase concentration drained from the peripancreatic area for more than 7 days.

Other complications were recorded on a free format. The duration of surgery, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization.

### Sample Size

The projected 5-year survival rates for groups A and B patients were 50% and 62%, respectively, and we initially planned to recruit 412 patients (206 each group) to detect this difference with one-sided $\alpha$ error of .05 and statistical power of 80%. At first, the recruitment was slow, but it improved as the study progressed. When the planned recruitment was almost achieved, the JCOG Clinical Trial Review Committee approved the amendment to increase the number of patients to 520 (260 each group) to

**Table 2.** Patients' Demographics and Tumor Characteristics

| | Group A (n = 263) | Group B (n = 260) | Total (N = 523) |
|---|---|---|---|
| Male-female ratio | 176/87 = 2.02 | 182/78 = 2.33 | 358/165 = 2.17 |
| Age, years | | | |
| Median | 60 | 61 | 61 |
| Range | 25-75 | 27-75 | 25-75 |
| Tumor diameter, cm | | | |
| Median | 5.5 | 5.5 | 5.5 |
| Range | 2-17 | 2-15.2 | 2-17 |
| T-stage (macroscopic) | | | |
| T2-SS | 99 | 93 | 192 |
| T3 | 150 | 159 | 309 |
| T4 | 14 | 8 | 22 |
| Tumor location | | | |
| Upper 1/3 | 53 | 47 | 100 |
| Middle 1/3 | 103 | 103 | 206 |
| Lower 1/3 | 107 | 110 | 217 |

NOTE. All data are numbers of patients except where otherwise indicated.
Abbreviation: SS, subserosal invasion.

enforce the statistical power to detect 8% difference in the 5-year survival rates, with a 5.5-year accrual period and an additional 5-year follow-up.

### Institutions and Quality Control of Surgery

The approval of the institutional review board from all participating institutions was obtained. Initially, the 12 institutions of the Gastric Cancer Surgical Study Group of the JCOG participated in the trial. Twelve institutions were added to increase patient recruitment before February 1999.

All participating surgeons agreed to the technical details for surgery during the planning stages of this trial. Significant experience in gastric cancer surgery, especially experience in extended lymphadenectomy, was a prerequisite for a surgeon's participation in the trial. Surgeons with experience of more than 100 D2 gastrectomies, or institutions with a specialized unit with annual gastrectomy volume of 80 cases or more were selected.

During the recruitment period, participating surgeons and Data Centre representatives met three times per year to monitor the study. In each meeting, videos of para-aortic dissection were presented for critique from four or five institutions, and the technical details were discussed. To assess compliance with lymphadenectomy, dissection, node recovery status in all nodal "stations," and the number of dissected nodes in the para-aortic area were recorded in the case report form, and the results were monitored.

### Statistical Methods

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between groups were evaluated using Fisher's exact test. Differences in length of hospital stay and blood loss were compared by Wilcoxon test. All $P$ values are two-sided, and statistical analysis was done using SAS (SAS Institute, Cary, NC) version 8.12.

## RESULTS

### Recruitment

Recruitment commenced in July 1995, and closed in April 2001. A total of 523 patients were enrolled: 263 in group A and 260 in group B. A large variance was observed for the number of patients recruited between the institutions. Fifty-three percent of all patients were recruited by the five major hospitals.

The JCOG site-visit audit reported that written consent was available for all except nine patients from one institution. In another institution, an additional six patients had informed consent submitted by a family member.

### Patients and Surgery

Patient demographics and tumor characteristics are presented in Table 2. The two groups were well balanced, as there were no significant differences in their baseline data.

The operative details are shown in Table 3. Total gastrectomy was performed in 38% of all patients, and the vast majority of total gastrectomies (186 of 199 cases) were accompanied by splenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor, accounting for 11% of all total gastrectomies. In four cases, proximal subtotal gastrectomy with splenectomy was performed instead of total gastrectomy. Para-aortic lymphadenectomy required longer operation time (median, 63 minutes) and resulted in greater blood loss (median, 230 mL) than the standard D2. Blood transfusion was required approximately twice as often.

### Protocol Violation and Ineligible Cases

There were 10 cases of protocol violation (1.9%). In one case, the para-aortic nodes were examined by frozen

**Table 3.** Operative Details

| | Group A (n = 263) | Group B (n = 260) | Total (N = 523) | P |
|---|---|---|---|---|
| Gastrectomy, No. of patients | | | | .62 |
| Total | 102 | 97 | 199 | |
| Distal subtotal | 160 | 160 | 320 | |
| Proximal subtotal | 1 | 3 | 4 | |
| Splenectomy, No. of patients | 98 | 93 | 191 | .79 |
| Pancreatectomy, No. of patients | 9 | 13 | 22 | .39 |
| Operation time, minutes | | | | < .001 |
| Median | 237 | 300 | 270 | |
| Range | 127-625 | 153-600 | 127-625 | |
| Blood loss, mL | | | | < .001 |
| Median | 430 | 660 | 530 | |
| Range | 32-1,810 | 60-2,885 | 32-2,885 | |
| Blood transfusion | | | | < .001 |
| No. of cases | 37 | 78 | 115 | |
| % | 14.1 | 30.0 | 22.0 | |
| No. of retrieved nodes | | | | < .001 |
| Median | 54 | 74 | 61 | |
| Range | 14-161 | 30-235 | 14-235 | |

section before registration. In another case, the surgeon performed para-aortic dissection despite the allocation to group A because after randomization, he found a positive node behind the common hepatic artery, believed to be strongly suggestive of metastasis in the para-aortic area. The postoperative course of this patient, who was allocated to group A but treated as group B, was uneventful, and analyzing this patient as either group A or group B had no effect on the results in this study. We left this case in group A based on intention-to-treat analysis. In the other eight patients, nodal stations No.13 and/or No.14v were not dissected in distal third tumors.

In another case, the initial histological diagnosis following endoscopic biopsy was poorly differentiated adenocarcinoma but the final histology of the resected stomach revealed gastric lymphoma. We included this patient in the morbidity/mortality analysis, but will exclude their data from the final survival analyses.

### Operative Morbidity

The overall operative morbidity rate was 24.5%. The morbidity for group B patients was higher than group A (28.1% and 20.9%, respectively), but the difference did not reach statistical significance ($P = .067$). The incidence of the four major surgical complications was not different between the two groups (Table 4).

There were various other complications reported, and the incidence was significantly higher in group B than group A patients. Paralytic ileus causing significant delay of recommencement of oral feeding, abdominal and/or left pleural lymphorrhea requiring prolonged drainage for more than 1 week, and severe diarrhea, were specific to the extended para-aortic dissection group (Table 4). Reoperation was needed in 12 patients (2.3%), and there was no difference in the reoperation rate between the two groups. Median hospital stay after surgery was 21 days in group A, and 24 days in group B ($P < .01$).

### Hospital Mortality

There were four hospital deaths (0.8%)—two in each group. Each group had one patient who died of postoperative complications, and one died of rapidly progressive cancer. All other patients recovered from surgery and were discharged from hospital.

## DISCUSSION

In this randomized controlled trial, the role of para-aortic dissection will be evaluated in terms of survival benefit,

**Table 4.** Operative Morbidity and Hospital Mortality

| | Group A (n = 263) | | Group B (n = 260) | | |
|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | P |
| Any complication | 55 | 20.9 | 73 | 28.1 | .067 |
| Anastomotic leak | 6 | 2.3 | 5 | 1.9 | .99 |
| Pancreatic fistula | 14 | 5.3 | 16 | 6.2 | .71 |
| Abdominal abscess | 14 | 5.3 | 15 | 5.8 | .85 |
| Pneumonia | 12 | 4.6 | 4 | 1.5 | .072 |
| Others | 24 | 9.1 | 52 | 20.0 | < .001 |
| Obstruction or ileus | 5 | | 11 | | |
| Lymphorrhea | 0 | | 10 | | |
| Left pleural effusion | 1 | | 6 | | |
| Severe diarrhea | 0 | | 3 | | |
| Reoperation | 5 | 1.9 | 7 | 2.7 | .57 |
| Hospital death | 2 | 0.8 | 2 | 0.8 | .99 |

operative morbidity/mortality, and quality of life. The results will provide important information and should guide decision making regarding the choice of operative methods. The quality of life and survival among these patients are still in the follow-up phase, and the analyses will take place in 2004 and 2006, respectively. This report compares the morbidity and mortality rates of D2 plus para-aortic node dissection with standard D2 dissection.

There is a wide variation in operative morbidity and mortality following gastric cancer surgery among countries and institutions. The presence of comorbid disease that affects patient fitness for surgery, surgical experience of the operator, and the workload volume seem to be important factors.[17,18] The mortality for gastrectomy in Western countries often exceeds 5% and approaches 16% in some series.[19-21] Conversely, Japanese studies have consistently reported a mortality rate of lower than 2% in retrospective observations. To date, the present study is the first large-scale prospective randomized controlled trial in Japan to compare surgical techniques under strict quality control and data management. The extremely low hospital death rate after extended para-aortic lymphadenectomy (0.8%) in this multi-institutional setting confirms the findings from previous retrospective reports.

This trial is a striking contrast to the the Dutch[4] and British[5] D1/D2 trials, in which D2 lymphadenectomy was associated with operative mortality rates of 10% and 13%, respectively. One important criticism of the European randomized trials was the issue of learning curve, as many British and Dutch surgeons participating in the trials were new to the D2 procedure. Surgical experience, specific anatomic knowledge, and careful postoperative managements by experienced teams are crucial to the success of this type of surgery. An Italian group appropriately carried out a phase 2 study of D2 lymphadenectomy in selected institutions[22] until an acceptable operative mortality rate was achieved, before conducting a randomized controlled trial comparing D1 and D2 gastrectomies.

The D2 gastrectomy procedure is known as "extended lymphadenectomy" in Western countries, while Japanese surgeons employ D2 as a standard technique, and reserve the term "extended" for para-aortic dissection. Lymphatic drainage from the stomach flows to the perigastric nodes and then to the nodes around the celiac axis and its main branches. From here it enters the para-aortic nodes before joining the systemic circulation via the thoracic duct. Hence, the para-aortic nodes may be regarded as the final station of nodes that can be dissected to remove the threat of systemic metastases originating from the lymphatic system. Many Japanese surgeons in specialized centers who performed para-aortic dissection found microscopic metastases in this region, and believe that this type of surgery may be potentially worthwhile. However, the risk associated with para-aortic dissection dictates advanced operative skills and intensive postoperative care. Therefore, scientific evidence supporting a survival benefit must be obtained before employing this technique in routine gastric cancer surgery.

The very low operative morbidity and mortality achieved in this JCOG trial can be attributed to several factors: (1) we selected a group of fit patients who could tolerate para-aortic dissection in the study. (2) Only specialist surgeons with an established track record of extended lymphadenectomy participated in the trial. (3) High-throughput centers were selected for their operative skills and standardized postoperative management. (4) Pancreatectomy was avoided whenever possible, while splenectomy accompanied total gastrectomy in most cases. We report that there was no significant difference in the overall complications between the two groups; however, the para-aortic dissection group had significantly higher "other" complications (on free format) compared with standard D2. Lymphorrhea and paralytic ileus were more specific to this operation. This observation may be biased because of the surgeon's awareness of the patient's randomization arm of para-aortic dissection.

In the British and Dutch trials, splenectomy with or without distal pancreatectomy was highlighted as a major risk factor for operative morbidity and mortality.[5,23] Total gastrectomy for proximal tumor requires more advanced surgical skill and is associated with a higher morbidity compared to distal gastrectomy. Proximal gastric tumors are rapidly increasing in number in the western countries,[24,25] while the incidence remains stable in Japan,[26] and this may partly explain the superior results obtained in Japanese studies. However, no difference was observed in the distribution of the primary tumor location between the Dutch[4] and the Japanese cohort. The proportion of total to distal gastrectomy was also very similar. Therefore, variation in tumor location and type of gastrectomy could not account for the difference in morbidity/mortality, at least between these trials. JCOG recently launched a randomized controlled trial to evaluate the role of splenectomy combined with total gastrectomy in proximal tumors.[27]

Gastric cancer, though decreasing in incidence worldwide, remains a major health problem in many countries. R0 (no residual disease) resection is the only curative measure; but the more extended the surgery, it is believed the greater is the risk of operative morbidity and mortality. The type of gastrectomy and the extent of lymphadenectomy must be carefully planned for each individual patient with gastric cancer. The Japanese guidelines clearly define D2 gastrectomy as standard surgery[28] based on the excellent results in Japanese studies, while the British cancer guidance[6] discourages D2 based on the poor results of their randomized trial. This contrast should be addressed by surgeons' efforts, such as establishment of specialized standard training systems or production of evidence by high-quality randomized trials in specialized centers.

In conclusion, this study has shown that specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Extending the surgery to para-aortic lymphadenectomy did not increase the major operative complications and hospital deaths. However, compared with the D2 procedure, para-aortic dissection requires a longer operation time, leads to a larger volume of blood loss, and longer hospital stay. Until survival benefits are clarified when the data mature sufficiently, para-aortic lymphadenectomy for gastric cancer should be regarded as experimental surgery[28] and only performed in specialized institutions within the context of a well-designed clinical trial.

## Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

## Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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*Review article*

# TNM and Japanese staging systems for gastric cancer: how do they coexist?

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**Abstract**
**Two staging systems for gastric cancer, International Union Against Cancer (UICC)/TNM and the Japanese classification, have been used widely for clinical practice and research. The two systems started independently in the 1960s, and underwent several revisions and amendments in order to approach each other, but have become more divergent in the latest editions because of characteristics based on different philosophies. The TNM system adopted a number-based system for N-staging that provides easy and accurate prognostic stratification. Comparative studies have shown that the TNM system has greater prognostic power than the Japanese classification. It contains, however, no treatment guidance and should primarily be used as a guide to prognosis. In contrast, the Japanese classification has been designed as a comprehensive guide to treatment, originally for surgeons and pathologists, and today for oncologists and endoscopists as well. Its anatomical-based N-staging was established based on analysis of lymphadenectomy effectiveness, and naturally provides direct surgical guidance. Clinicians should understand the roles of each system and must not mix the systems or terminology when they report their study results.**

**Key words** Stomach neoplasms · Classification · TNM · Japanese classification · Stage

## Introduction

Gastric cancer is the world's second commonest cancer, superseded only by lung cancer in this undesirable world ranking. While the incidence of gastric cancer continues to decline steadily in the West, it is still the commonest malignancy in Japan. However, the chance of cure from the disease remains highest in Japan, where there has been a steady improvement in survival rate over the past three decades. Much of this is due to increased diagnosis of early gastric cancer, which accounts for half of all cases, as well as more radical intervention for advanced disease. By contrast, the majority of the cases in the West present late with advanced disease, and there has not been a significant improvement in the overall survival, despite improvements in surgical technique.

Narrowing the gap between Western and Japanese outcomes will probably require changes at many levels. However, attempts to compare gastric cancer outcomes have been hampered by differences in both the philosophy and practicality of staging the disease in Japan and the West [1].

The two main staging systems for gastric cancer are the TNM staging system of the International Union Against Cancer (UICC), and the Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association (JGCA). Similarities between these two staging systems exist; namely, that staging is dependent on the extent of the primary tumor, the extent of lymph node involvement, and the presence or absence of distant metastasis. However, there still remain fundamental differences between the two staging systems. The most recognizable difference lies with the classification of regional lymph node spread. The UICC/TNM staging system divides N stage on the basis of the number of metastatic lymph nodes, while the Japanese classification stresses the location of involved nodes.

Staging has a variety of functions, which should be reflected in the staging systems used. In addition to providing an indication of prognosis, staging should ideally be able to provide a framework for treatment decisions, and should allow for evaluation of treatment with meaningful comparisons between different treatments or the same treatment modalities by different groups.

The purpose of this review is to outline the philosophy, background, and major features of the current staging systems and to assess their suitability to serve the above functions.

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## Two main classifications

The current main classification systems for gastric cancer are the sixth edition of the UICC/TNM classification (2002) [2] and the thirteenth edition of the *Japanese classification of gastric carcinoma* (second English edition [3] (1998), downloadable from http://www.jgca.jp/PDFfiles/JCGC-2E.PDF), herein referred to as the JGCA classification. Other systems have been proposed, which will be discussed briefly later in the text.

### *UICC/TNM classification*

In 1954, the UICC appointed a Committee on Tumor Nomenclature and Statistics, which subsequently agreed on a technique for classification of cancer according to the anatomical extent of the disease. Gastric cancer was first included in the TNM staging system in 1966. There have been relatively few revisions to the UICC classification, which is now still only in its sixth edition.

The UICC/TNM system was originally a purely clinical classification, so that a disease stage could be decided before any treatment. In gastric cancer, however, surgical findings were indispensable for classification, because the principal prognostic factors were diagnosed only after surgical exploration. The American Joint Committee on Cancer Staging and End Results Reporting (AJCC) was organized in 1959 to develop a staging system acceptable to the American medical profession, basically using the UICC/TNM format. In 1970, the AJCC published a TNM-based staging system, using clinical, surgical, and histological information [4]. The background database was from 1241 patients with gastric cancer, which had been analyzed by a task force from seven American institutions. The system used penetration of stomach wall (T), proximity to the primary cancer of metastatic perigastric lymph nodes (N), and presence or absence of distant metastases (M), including nodes not in the perigastric area, as these criteria had the greatest impact on outcome in the above cohort.

The third edition of the UICC/TNM in 1978 contained a unified classification with the AJCC. The T stage was defined by stomach-wall invasion, but the "clinical T" and "pathological T" had different definitions. The N stage was defined by anatomic location of nodes from N0 to N3. N1 nodes were defined as metastatic perigastric nodes within 3 cm of the primary, and N2 nodes were nodes beyond 3 cm from the primary, or along the celiac, splenic, left gastric, or hepatic arteries. N3 nodes were paraaortic and hepatoduodenal nodes. In the fourth of the TNM classification edition (1987), T stage was unified to the style of the current edition, and the N3 category was dropped and reclassified as M1 (Table 1).

**Table 1.** TNM classification, 4th edition; 1987

| | | M0 | | | M1 |
|---|---|---|---|---|---|
| | | N0 | N1 | N2 | |
| M0 | T1 | IA | IB | II | |
| | T2 | IB | II | IIIA | |
| | T3 | II | IIIA | IIIB | |
| | T4 | IIIA | IIIB | | |
| M1 | | | | | IV |

N1, perigastric nodes within 3 cm of the primary tumor; N2, nodes beyond 3 cm from the primary, or along the celiac, splenic, left gastric or hepatic arteries

**Table 2.** TNM classification, 5th edition; 1997

| | | M0 | | | | M1 |
|---|---|---|---|---|---|---|
| | | N0 | N1 | N2 | N3 | |
| M0 | T1 | IA | IB | II | | |
| | T2 | IB | II | IIIA | | |
| | T3 | II | IIIA | IIIB | | |
| | T4 | IIIA | | | | IV |
| M1 | | | | | | |

N1, 1–6 involved nodes; N2, 7–15 involved nodes; N3, >15 nodes

The fifth edition (1997) of the TNM classification contains several amendments from the previous edition. The greatest change was that, whereas previously N status was determined by the anatomical site of involved lymph nodes, in the new classification, N stage is determined by the number of metastatic lymph nodes from a minimum yield of 15 lymph nodes in total (N1, 1–6 involved nodes; N2, 7–15 involved nodes; and N3, >15 nodes; Table 2). This had been explored as an option for some time and a proposal to add the number of involved lymph nodes to the anatomical-based N stage was published by the UICC in 1993 [5]. The idea of adopting a number-based N-staging for gastric cancer had also been proposed by some Japanese surgeons [6,7]. Data from a German multicenter gastric cancer study showed the effectiveness of the new proposal in providing better prognostic stratification than previous systems [8].