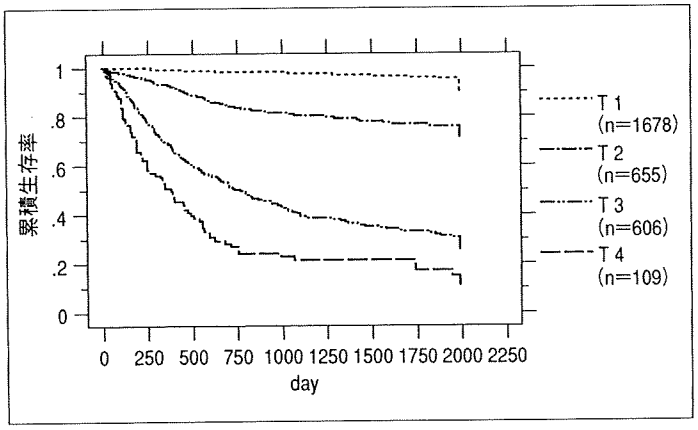

図6a 『胃癌取扱い規約（第13版）』T因子による分類（全例）

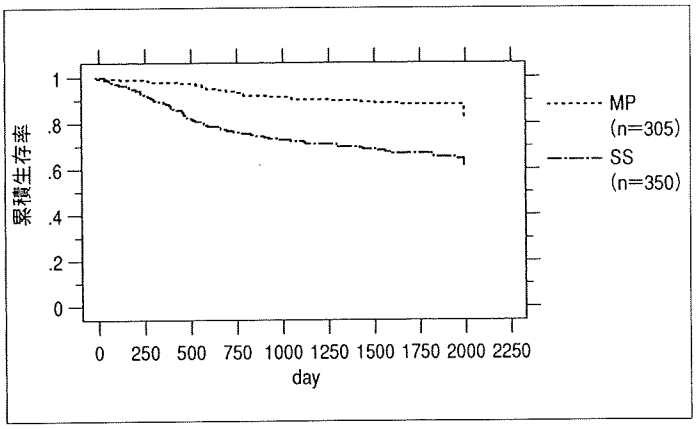

図6b MP vs SSの比較

針としてより理解しやすい分類となることが望ましい。また「胃癌規約」のT2も，「TNM」のようにT2a（MP），T2b（SS）と亜分類，もしくは大腸癌のように，T2（MP），T3（SS）と分類される可能性は高く，これが病期にかかわってくる可能性もある。

歴史的には，外科を中心にして，胃癌の臨床病期分類が作成・改訂されてきたが，胃癌に対する化学療法はTS-1，CPT-11，Taxan系と新たに効果のある薬剤が使われるようになり，ここ数年で著しく進歩してきた。また分子標的治療薬も加わって，化学療法の重要性がいっそう増すものと思われる。現行の病期分類は，「胃癌規約」，「TNM」ともに化学療法によく対応していないため，国際的な薬物・放射線療法の評価法として用いられているresponse evaluation criteria in sorid tumors（RECIST）との不整合性が問題となっている[24)25)]。また臨床病期分類は，初期治療施行前の患者の評価であり，術前治療が行われた場合の病期をどのように評価するかがはっきりと規定されていないことも検討すべき問題である。

臨床病期は，内視鏡（高解像度，拡大など），CT（3D-CTなど），超音波内視鏡，PETなど多様なmodalityにより精度の向上が図られており，臨床病期分類は，将来的にはこれらの詳細な画像診断に加えて，治療効果予測にかかわる生検診断，遺伝子診断なども考慮した改訂が必要になると推測される。さらに微小転移やITCの扱い方についても考慮を要する。このような診断精度の向上を踏まえ治療成績を取り直すことで，新しいデータの蓄積がすすみ，病期分類は再び改訂を求められるようになるであろう。

まとめ

わが国における癌取扱い規約の目的は，多数施設からの多数症例（登録例）に基づく，信頼性の高い臨床病理学的データや手術成績をだすこと，さらに施設間のデータ比較を確実・容易にすることにある。そのために，手術方法，検索方法，所見の判定法，成績の算出法などの基準・記載法を統一する必要があり，直接の目的はここにあると考える。実際，わが国の癌治療が外科医を中心に行われてきた歴史も反映して，癌取扱い規約は単に臨床病期や治療成績を示すだけでなく，手術治療の指針となる要素が大きかった。このことは，『胃癌取扱い規約』，『食道癌取扱い規約』のいずれにおいても，N分類として，リンパ節の解剖学的分類が行われ，手術における郭清範囲が定められていることからも容易に想像がつく。そして，このことが，欧米の臨床病期分類とわが国の癌取扱い規約の大きな相違点であり，問題点となっていることは既述のとおりである。癌取扱い規約がこのような性格をもつために，治療法の進歩や多様化に従って，きわめて複雑化しているのも事実である。しかし，本来，このような基準・記載法は，できるだけ単純であるべきであり，診断・治療に関する部分に関しては，近年，多く出版されている診療ガイドラインとの棲み分けを図る必要がある。

食道癌，胃癌の診断・治療が刻々と進歩するなかで，それらの病期分類もより正確な予後の予測と治療方針の指標となるべく，変化が求められている。とくに化学療法，化学放射線療法などの有効性が示されている現在，術前治療を踏まえた病期分類なども考慮していく必要性が出てきた。組織型，遺伝子診断，そして微小転移などを今後病期分類にどう組み込んでいくかも今後の課題である。病期分類は，いずれにしても，ほかの癌規約やTNM分類との整合性を考慮すべきであり，種々の工夫がなされる必要がある。もちろん，わが国の癌取扱い規約とAJCC/UICCのTNM分類は，おのおのが社会的・医学的背景を踏まえ成立してきたもので，完全な一致をみる必要はないと考えるが，

診療・研究の国際的標準化を図るうえでは，これらの分類の相互参照・協調による歩み寄りが必要である。そのためにも，わが国からのより積極的な国際的アプローチを行うべきである。

今般のAJCCのTNM分類の改訂に際し，本検討でも用いた癌研の胃癌データを用いて，日本の治療成績もある程度反映させた癌研有明病院の佐野武先生と関係諸先生方の努力に敬意を表する。

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7．左上腹部内臓全摘術

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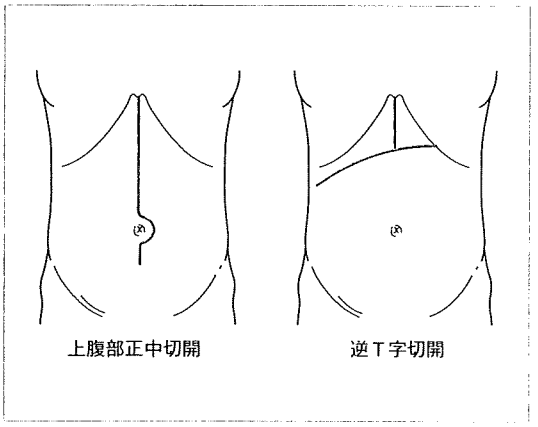
はじめに

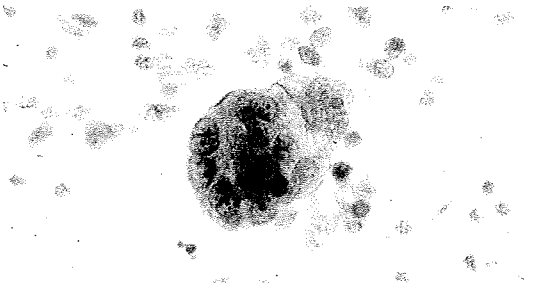
左上腹部内臓全摘術は胃とその隣接臓器を一括して癌とともに摘除する拡大手術である[1]．胃全摘に膵体尾部，脾臓，横行結腸と結腸間膜，胆嚢，左副腎などを合併切除するが，最大の特徴は網嚢を取り囲む臓器を袋状に一塊として摘出できることである．特に横行結腸間膜全層と膵体尾部を連続して摘出することにより進行胃癌の浸潤部位をより根治的に摘除できるところが，ほかの術式と異なる点である．筆者らは左上腹部内臓全摘術にAppleby手術を加えた手術も行っているが[2,3]，ここでは左上腹部内臓全摘術だけに関して，胃全摘・膵脾合併切除と異なる手技を中心にそのコツを述べる．

1．皮膚切開

開腹は剣状突起より臍下5cmに至る上腹部正中切開で行う（図1）．吊り上げ式開創器を用いるので，正中切開でも上腹部の広い術野の展開が可能である．また，左上腹部内臓全摘術では右半結腸を左方へ脱転するが，臍下に延長した開腹創により，この操作も安全に行うことができる．一方，横切開の変法である逆T字切開を行っているところもある[1]．



[図1] 皮膚切開


[図2] 腹腔内洗浄細胞診（×400）

2．腹腔内洗浄細胞診

4型（スキルス）胃癌などのように漿膜浸潤範囲が広い進行胃癌では，いきなり開腹せずに，まず診断的腹腔鏡検査を行い腹膜転移の有無を確認する．一方，切除予定で開腹した場合は，開腹直後に腹腔内を観察して腹膜転移の有無を確認する．Douglas窩に腹水があれば腹水を，なければ横行結腸より下部の腹腔内に生理食塩水100mlを注入して攪拌した後にDouglas窩から採取する．遠隔腹膜転移陽性あるいは腹腔内洗浄細胞診陽性であれば手術の適応はない（図2）．手術適

応を決定するためにきわめて重要な検査であるので，この細胞診は開腹後直ちに行う．

3．胃結腸静脈幹（Henle幹）の切離

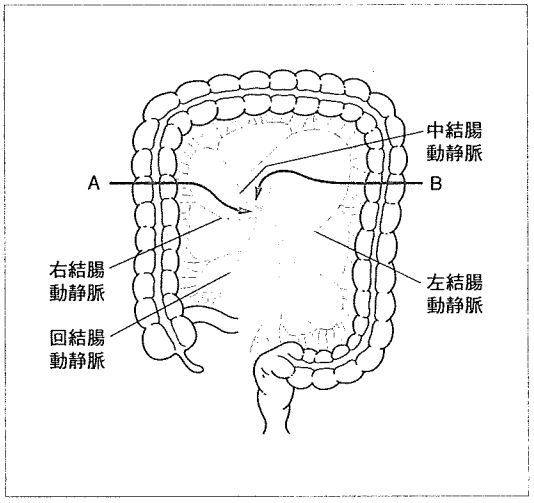
上行結腸の授動・遊離をTreitz靱帯方向へ進める．助手が結腸を牽引して，fusion fasciaとsubperitoneal fasciaの間を剝離していくが，深く入って尿管を損傷しないように気をつけなければならない．上行結腸を遊離したら，回結腸動静脈，右結腸動静脈の走行を確認する．結腸肝曲部の切離に際しては右結腸動脈を温存するが，右結腸動脈は中結腸動脈と共通幹を形成していることも多く，横行結腸切除では中結腸動脈を切離するので残存結腸の血流をよく考慮して切離部位を決定する．75mmの自動縫合器を用いて結腸肝曲部を切離した後に，そこから結腸間膜を根部に向かって切り開き（図3の矢印A），膵頭十二指腸の外側下縁からその前面を膵切痕に向かって腹膜を剝離していくと，胃結腸静脈幹（Henle幹）に到達する（図4）．

左上腹部内臓全摘術は，胃と結腸を別々に取るのではなく，胃と結腸を網嚢とともに一塊として摘出する術式であり，横行結腸の前面からその血管を処理しないで，図4のように横行結腸間膜の後面から切離し，網嚢を破らないようにする．右胃大網静脈と中結腸静脈が合流して胃結腸静脈幹（Henle幹）になり上腸間膜静脈に流入するが，前膵十二指腸静脈弓も含めて種々の走行がみられるので，膵頭十二指腸の外側下縁からその前面を膵切痕に向かって腹膜を剝離していくことがコツである．

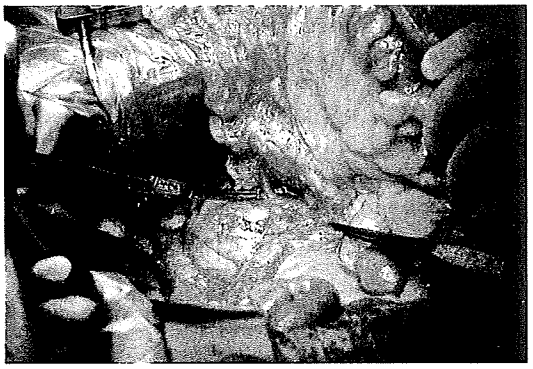
［ポイント］胃結腸静脈幹の切離には，膵頭部下縁から前面を膵切痕に向かって剝離

4．中結腸動脈の切離

下行結腸を授動して，左結腸動脈の走行を確認する．中結腸動脈左枝の末梢と左結腸動脈の末梢との吻合部をよく観察し，残存する下行結腸の血流を考慮して切離部位を決定する．脾曲部結腸の



［図3］横行結腸切除と胃結腸静脈幹・中結腸動脈の切離


［図4］胃結腸静脈幹（Henle幹）の切離


［図5］中結腸動脈の切離（結腸間膜中央の陥凹は癌浸潤）

血流は通常微弱であることが多く，脾曲部を越えた下行結腸で切離することになる．筆者らは，手縫いの時期も含めて左上腹部内臓全摘術において結腸吻合部の縫合不全を1例も経験していないが，血流状況を評価して結腸切離部位を決定することが重要と考える．75mmの自動縫合器を用いて脾曲部末梢で結腸を切離した後に，そこから結腸間膜を根部に向かって切り開き，中結腸動脈根部に達する（図3の矢印B）（図5）．

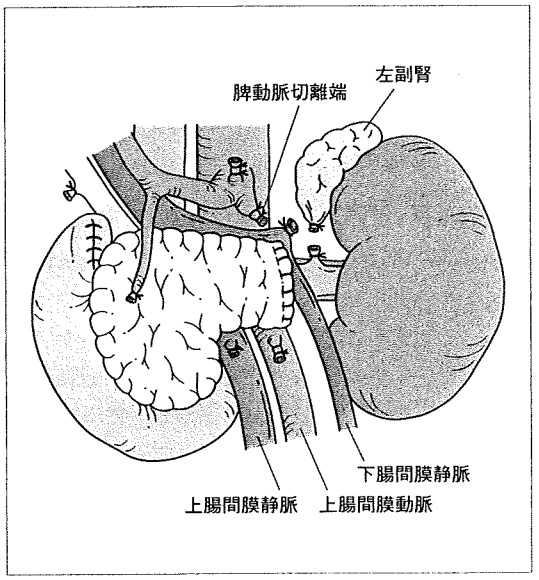
中結腸動脈を二重結紮して切離する．この時点で網嚢は胃，膵臓，結腸間膜，横行結腸，大網，脾臓などとともに破られずに袋状を維持している．

［ポイント］結腸の切離部位は血管走行を確認して血流優先で決定

5. 膵体尾・脾・横行結腸間膜・横行結腸・全胃を一塊として摘出

膵体尾・脾を横行結腸間膜とともに摘出するので，膵尾部の被膜は剝離しない．膵体部および膵頭部前面の被膜を剝離して，胃十二指腸動脈を露出する．この胃十二指腸動脈を末梢方向に追跡して，右胃大網動脈を根部で切離する．胆嚢摘除，右胃動脈切離，No.12・No.13リンパ節を郭清し，十二指腸を切離する．No.8・No.9リンパ節の郭清，左胃動脈の切離が終わると，脾動脈を根部で結紮切離する．膵脾を脱転し，膵臓を後面から観察して脾静脈が下腸間膜静脈と合流する部位で脾静脈を結紮切離する．この下腸間膜静脈合流部の位置で膵臓を切除する．膵管を確実に結紮した後に膵断端を魚口形に縫合閉鎖する．あとは胃全摘と同じ手順で食道を切除する．膵体尾・脾・横行結腸間膜・横行結腸・全胃が一塊として摘出される（図6）．

左副腎の摘除は本術式の必須手技ではない．筆者らは4型（スキルス）胃癌に対して，後腹膜癌浸潤を除去する目的もあり左副腎の摘除を行っているが，前出の一括切除臓器とは別に操作している．No.16 a2 latリンパ節郭清は左副腎摘除により確実に行えるが，図6のように左副腎温存・副腎静脈切離でも十分な術野を確保することが可能



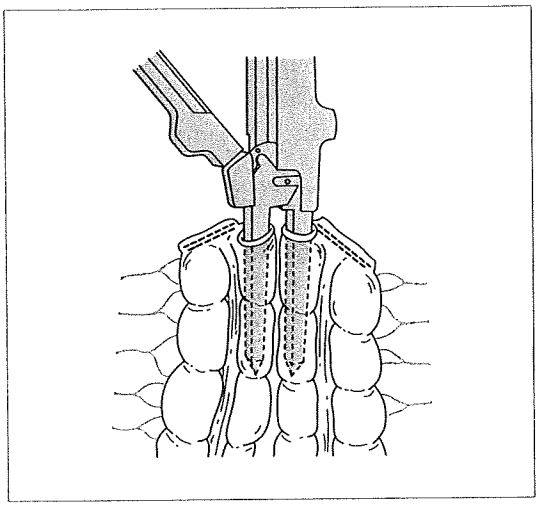
［図6］左上腹部内臓全摘術後の腹腔内

となる．しかし，このような左副腎温存の方法は，必ずしも機能するとは限らないので，摘除する場合と同様に，術前にCTなどで右副腎に転移などの異常所見のないことを確認しておく必要がある．

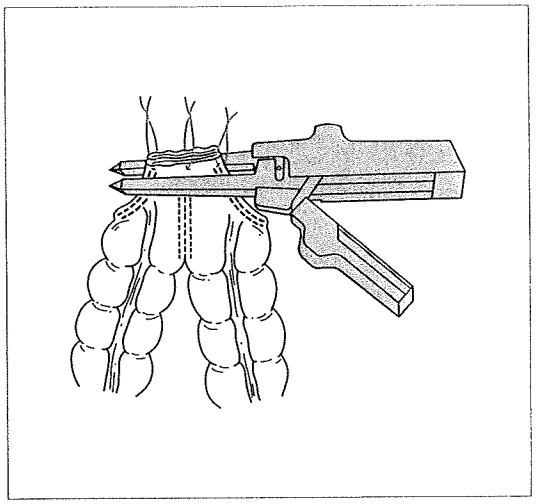
6. 結腸のfunctional end-to-end anastomosis

横行結腸切除後の結腸吻合には器械を用いる．十分な血流を確認した部位で切除しておけば手縫いでも縫合不全の発生をみないが，器械吻合のほうが技術が一定し，時間の短縮にもなる．回盲部を完全に遊離してあるので，吻合部は左上腹部に位置する．横行結腸切除時に75mmの自動縫合器を2回用いたが，これらのステープルの一部は吻合部に残ることになる．腸間膜付着部対側で，縫合器を入れる穴を開けて挿入する（図7a）．腸のねじれを補正して縫合切離する．ここで用いた器械は腸管内で汚染されているので，腸液を除去して0.5%グルコン酸クロルヘキシジン水溶液に30秒間浸し，その後この消毒薬を洗浄する[4]．な

◎左上腹部内臓全摘術は，網嚢を取り囲む臓器を袋状に一塊として摘出．
◎結腸の切離部位は血管走行を確認して血流優先で決定．
◎結腸吻合は正中ではなく左上腹部に位置するようにし，器械吻合．



[図7a] 結腸の functional end-to-end anastomosis その1



[図7b] 結腸の functional end-to-end anastomosis その2

お，長い柄のついたカートリッジ4本がキットになった functional end-to-end anastomosis 専用の製品も市販されており，これを用いればこのような消毒作業は不要となる．2本の挿入部は一つの大穴になり，これを再び器械で閉鎖するが，1回目のステープル同士が重ならないようにずらして支持し，縫合切離する（図7b）．漿膜筋層縫合の追加は縫合不全の防止に有用で，少なくともステープルが重複する部位は必須である．

［ポイント］結腸吻合は正中ではなく左上腹部に位置するようにし，器械吻合

おわりに

左上腹部内臓全摘術が胃全摘・膵脾合併切除と異なる点は，横行結腸間膜全層と膵体尾部を連続して摘除できることである．横行結腸間膜の後面で中結腸動静脈を根部で切離することが重要であり，それからの操作は胃全摘・膵脾合併切除とほとんど同じである．

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Original article

Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer

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Background: Locally advanced gastric cancer with extensive lymph node metastasis is usually considered unresectable and so treated by chemotherapy. This trial explored the safety and efficacy of preoperative chemotherapy followed by extended surgery in the management of locally advanced gastric adenocarcinoma.

Methods: Patients with gastric cancer with extensive lymph node metastasis received two or three 28-day cycles of induction chemotherapy with irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent gastrectomy with curative intent with D2 plus para-aortic lymphadenectomy. Primary endpoints were 3-year overall survival and incidence of treatment-related death.

Results: The study was terminated because of three treatment-related deaths when 55 patients had been enrolled (mortality rate above 5 per cent). Two deaths were due to myelosuppression and one to postoperative complications. Clinical response and R0 resection rates were 55 and 65 per cent respectively. The pathological response rate was 15 per cent. Median overall survival was 14·6 months and the 3-year survival rate 27 per cent.

Conclusion: This multimodal treatment of locally advanced gastric cancer provides reasonable 3-year survival compared with historical data, but at a considerable cost in terms of morbidity and mortality.

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Introduction

Macroscopically complete tumour removal is a prerequisite to cure gastric cancer[1,2]. Japanese surgeons have explored the benefits and disadvantages of para-aortic nodal dissection for locally advanced tumours with nodal metastases[3–6]. The Japanese Gastric Cancer Association (JGCA) defines para-aortic lymph nodes as being regional lymph node stations (JGCA-N3)[7]. Tumours with bulky nodal metastases surrounding the coeliac artery and its branches (JGCA-bulky N2) are usually considered unresectable. The prognosis of patients with JGCA-N3 or JGCA-bulky N2 is extremely poor even when the entire tumour and lymph nodes can be resected with curative intent. Further, complete resection of these tumours often requires combined organ resection, such as distal pancreatectomy, resulting in major surgical complications[8]. Even after this surgery with curative intent, most tumours recur, suggesting that distant micrometastases were already present.

In contrast to the Japanese staging system, the tumour node metastasis (TNM) staging of the International Union Against Cancer (UICC) defines para-aortic metastases as

The Editors are satisfied that all authors have contributed significantly to this publication

distant metastases[9]. In Western countries, tumours with JGCA-N3 or JGCA-bulky N2 are therefore regarded as unresectable disease that warrants palliative chemotherapy. These patients rarely survive for more than 3 years when they receive chemotherapy alone or when surgery is followed by postoperative chemotherapy. To improve this dismal prognosis, a different strategy should be developed.

Preoperative chemotherapy has some theoretical benefits in these patients in comparison with postoperative chemotherapy. First, extended surgery can be performed easily and safely because the chemotherapy usually leads to shrinkage of lymph nodes, increasing the likelihood of R0 resection. Second, more intensive chemotherapy is possible with high compliance. Third, distant micrometastases can be treated early, before local therapy has begun. Recently, the effectiveness of a regimen of preoperative and postoperative epirubicin, cisplatin and infused fluorouracil for less advanced disease was suggested[10]. Combined chemotherapy using irinotecan hydrochloride plus cisplatin is also an attractive regimen for preoperative chemotherapy. In a phase II trial using this regimen in patients with metastatic gastric cancer, a response rate of 48 per cent and acceptable toxicity were reported[11].

The present study was conducted to evaluate the efficacy and safety of preoperative chemotherapy with irinotecan plus cisplatin followed by gastrectomy with D2 plus para-aortic nodal dissection for locally advanced gastric cancer with extensive lymph node metastases.

Methods

The study was conducted as a prospective multi-institutional phase II trial between 2000 and 2003 involving the 21 institutions of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with locally advanced gastric cancer presenting at their institution were considered for participation in the study. The absence of peritoneal dissemination was confirmed by laparoscopy before entry into the study.

Eligibility criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; para-aortic nodal metastases and/or bulky N2 cancers confirmed by contrast-enhanced computed tomography (CT) (definitions in *Fig. 1*); no metastases outside the para-aortic region, as confirmed by contrast-enhanced CT; no peritoneal or pleural effusion; no

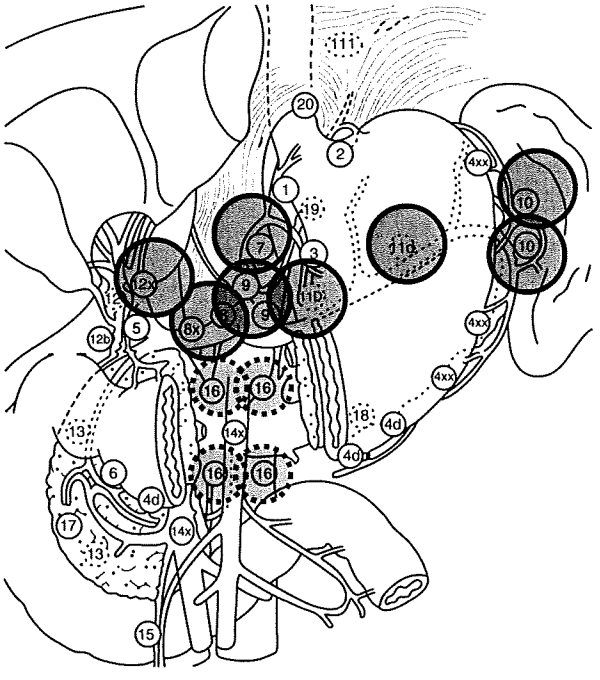

Fig. 1 Definitions of bulky N2 and para-aortic nodal metastases. Bulky N2 (in solid circles): at least one node of 3 cm or more in diameter, or at least three consecutive nodes each of diameter 1·5 cm or more, along the coeliac, splenic, common or proper hepatic arteries. Para-aortic nodes (in dashed circles): at least one node of 1 cm or more in diameter around the abdominal aorta

clinically apparent brain or bone metastases; no peritoneal metastases and negative cytology at laparoscopy; non-scirrhous type macroscopically; 20–70 years of age; Eastern Cooperative Oncology Group performance status 0 or 1; no previous chemotherapy or radiotherapy. In addition, patients had to have no signs of organ failure, as assessed by a white blood cell (WBC) count minimum of 4000/mm^3 and maximum of 12 000/mm^3, platelet count of 100 000/mm^3 or above, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than three times the upper limit of normal, total bilirubin 1·5 mg/dl or less, creatinine 1·2 mg/dl or less and creatinine clearance 60 ml/min or above, and haemoglobin 9·0 g/dl or more. There had to be no ischaemic change or ventricular arrhythmia on exercise electrocardiography, a forced expiratory volume in 1 s of 50 per cent or more, arterial partial pressure of oxygen (PaO_2) of 70 mmHg or above, and indocyanine green test in 15 min of 10 per cent or less in cases of liver dysfunction, negative serology for viral hepatitis and no past history of hepatitis. All patients gave written informed consent.

Exclusion criteria included: active gastrointestinal bleeding, infection, watery diarrhoea, synchronous or metachronous (within 10 years) malignancy other than carcinoma *in situ*, pregnancy or lactation, treatment with a major tranquillizer, lung fibrosis or interstitial pneumonitis, and bowel obstruction. Patients with allergic reactions to iodine were excluded because contrast-enhanced CT could not be performed. All patients were registered centrally at the JCOG Data Centre, where data management, central monitoring and statistical analysis were conducted. For quality assurance, a site visit audit was performed by the JCOG Audit Committee.

Preoperative chemotherapy

Irinotecan 70 mg/m^2 was administered on days 1 and 15 and cisplatin 80 mg/m^2 was given on day 1 as one course, repeated every 4 weeks[11]. If the patient had a WBC of 4000/mm^3 or less, platelet count of 10 000/mm^3 or lower, diarrhoea of grade 1 or above (increase of four or more stools per day over pretreatment), an episode of infection or abnormal serum creatinine concentration, administration of irinotecan and/or cisplatin was postponed until recovery. If recovery did not occur within 2 weeks, chemotherapy was stopped. On day 15 of each course, if the patient had an adverse event the second administration of irinotecan was postponed, and was not given if the adverse event was still observed on day 22. If the patient had haematological adverse events of grade 4 (haemoglobin level less than 6·5 g/dl, leucocyte count below 1000/mm^3, neutrophil count less than 500/mm^3, or platelet count below 25 000/mm^3), diarrhoea of grade 3 or higher (increase of more than seven stools per day or incontinence, or need for parenteral support for dehydration), or if the second administration of irinotecan was not given in the last course, the next dose of irinotecan was reduced to 60 mg/m^2. If the patient had a serum creatinine level of 1·2–1·5 mg/dl, the next dose of cisplatin was reduced to 60 mg/m^2. If serum creatinine was 1·5 mg/dl or above, initiation of the next course was delayed.

Some 7–13 days after the second administration of irinotecan in each course, resectability was evaluated based on CT findings by the Response Evaluation Criteria in Solid Tumours (RECIST)[12]. If curative resection was considered possible after the second course, the patient had surgery immediately. If curative resection was considered difficult, a further course of chemotherapy was added before surgery.

Surgery

Resection criteria included: R0 resection deemed possible by gastrectomy with D2 plus para-aortic nodal dissection, and no evidence of organ failure as assessed by a WBC count greater than 3000/mm^3 and less than 12 000/mm^3, platelet count above 100 000/mm^3, AST and ALT levels less than three times the upper limit of normal, total bilirubin less than 1·5 mg/dl, creatinine below 1·5 mg/dl and creatinine clearance above 50 ml/min, and PaO_2 greater than 70 mmHg. Eligible patients were operated on 3–6 weeks after chemotherapy.

After laparotomy, resectability was again evaluated and, if intraperitoneal wash cytology was negative, R0 resection was attempted by gastrectomy with D2 plus para-aortic nodal dissection, as described previously[13]. If necessary, D2 plus para-aortic nodal dissection was combined with splenectomy and/or distal pancreatectomy.

The treatment protocol was completed when a patient had received two or three courses of preoperative chemotherapy and had undergone R0 resection by gastrectomy with D2 plus para-aortic nodal dissection (*Fig. 2*). After completion of the protocol, no further treatment was given until tumour recurrence.

Quality control of surgery

During the recruitment period, participating surgeons and data centre representatives met three times per year to monitor the study. At each meeting, videos of various surgical procedures, including nodal dissection, were presented by several participating institutions,

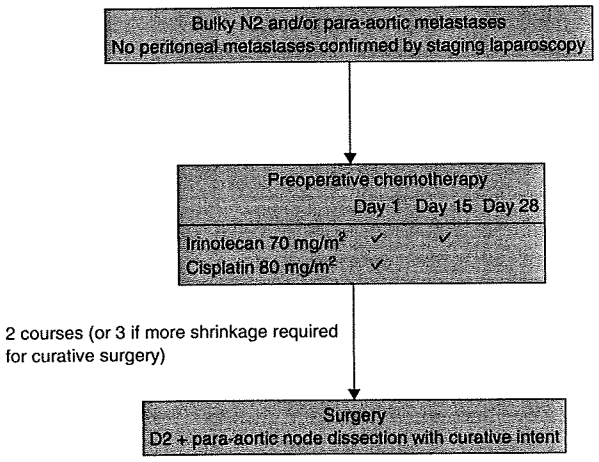

Fig. 2 Study outline

and technical details were discussed for critique. To assess compliance with lymphadenectomy, the number of dissected nodes was recorded.

Objectives and evaluation

Primary endpoints were overall survival and incidence of treatment-related death. Secondary endpoints were number of R0 resections, response to chemotherapy, chemotherapy-related toxicity and surgical complications. Clinical response was evaluated by RECIST[12], based on CT with a central review. Surgical specimens were evaluated pathologically and graded according to the proportion of tumour affected by degeneration or necrosis[14]: grade 0, no part of tumour affected; grade 1a, less than one-third affected; grade 1b, between one-third and two-thirds affected; grade 2, between two-thirds and entire tumour affected; and grade 3, no residual tumour. A pathological response was defined as one-third or more of the tumour affected (grade 1b, 2 or 3). Adverse events during chemotherapy were evaluated by the National Cancer Institute – Common Toxicity Criteria version 2.0[15].

Statistical analysis

For sample size calculation, treatment was considered effective if the lower limit of the 95 per cent confidence interval (c.i.) for 3-year survival exceeded 15 per cent. In terms of feasibility and efficiency, sample size was determined as 60 with a 3-year entry and 3-year follow-up period. In this setting, the exact binomial lower confidence limit for a 3-year overall survival rate of 30 per cent (18 of 60) was 18·9 per cent and that for 25 per cent (15 of 60) was 14·8 per cent. This was considered sufficiently precise to make inferences based on 3-year survival. Hence, the sample size was calculated as 60.

The survival curve was estimated using the Kaplan–Meier method; 95 per cent c.i. were calculated with the Greenwood formula[16]. Treatment was considered safe if point estimates of treatment-related death did not exceed 5 per cent. The stopping rule for safety was prespecified so that the study would be terminated when treatment-related death had been observed in three patients (treatment-related death exceeding 5 per cent). Statistical analysis was performed with SAS® version 8.2 (SAS Institute, Cary, North Carolina, USA). This phase II trial was approved by the JCOG Protocol Review Committee and institutional review board of each institution involved.

Results

Between August 2000 and May 2003, 55 patients were entered into the study and underwent preoperative chemotherapy. All patients were followed for more than 3 years after registration. When 55 patients had been registered, three were judged as treatment-related deaths by the JCOG data and safety monitoring committee, and the study was terminated according to the stopping rules. Thus, the treatment-related death rate was 5 (95 per cent c.i. 1 to 15) per cent. *Table 1* shows patient demographics and tumour characteristics. A flow diagram from chemotherapy to surgery is shown in *Fig. 3*. The clinical response rate for all eligible patients was 55 (95 per cent c.i. 41 to 68) per cent (30 of 55 patients) (*Fig. 3*).

Table 1 Demographics and tumour characteristics in 55 eligible patients

Median (range) age (years)	63 (46–70)
Sex ratio (M : F)	42 : 13
ECOG performance status	
0	47
1	8
Histology	
Differentiated	30
Undifferentiated	25
Nodal status	
Para-aortic nodes and bulky N2	19
Only para-aortic nodes	11
Only bulky N2	25

ECOG, Eastern Cooperative Oncology Group.

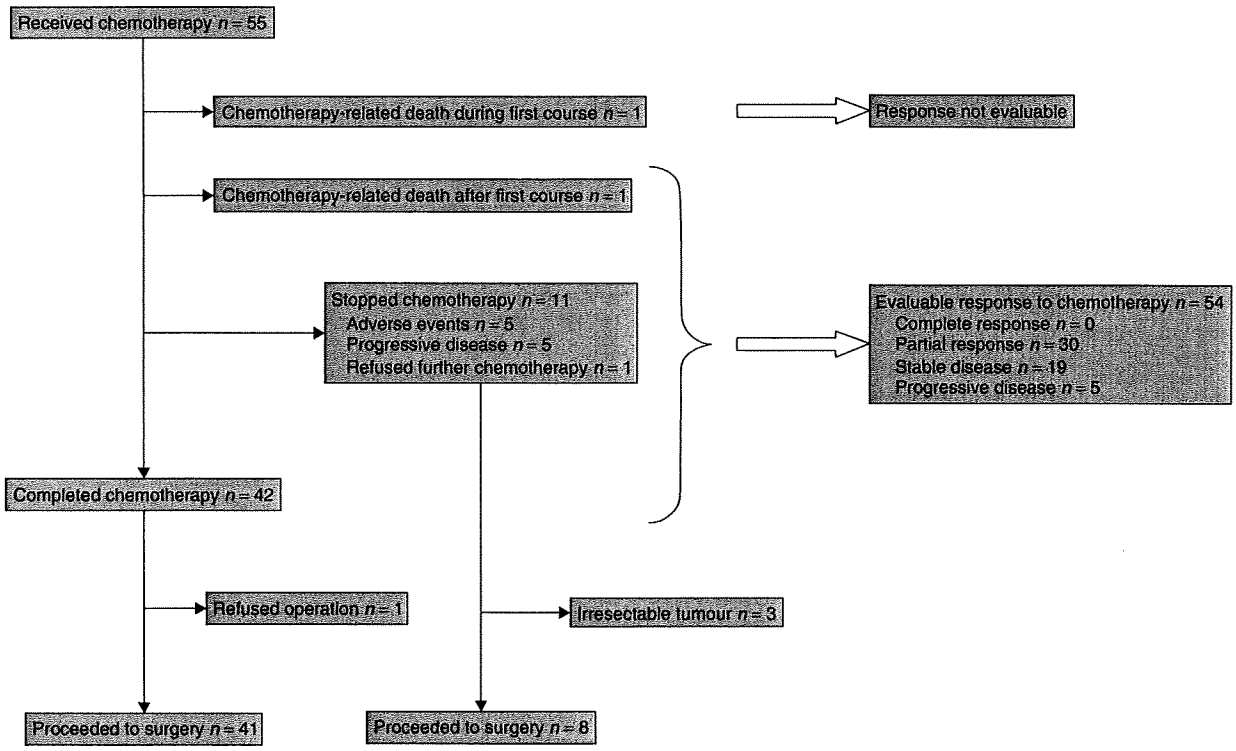

Fig. 3 Flow diagram from chemotherapy to surgery in 55 eligible patients

Table 2 Details of 49 patients who underwent surgery

	No. of patients
Peritoneal cytology	
Negative	45
Positive	4
Type of resection	
Total gastrectomy	32
Distal gastrectomy	15
Bypass	1
Exploratory laparotomy	1
Dissection of nodes along splenic artery	
With splenectomy and distal pancreatectomy	14
With splenectomy	16
Without splenectomy	13
No nodal dissection	6†
Operating time (min)*	370 (40–930)
Blood loss (ml)*	1050 (0–5650)
Blood transfusion	34
No. of para-aortic nodes dissected*	26 (0–86)
No. of nodes dissected*	87 (45–179)

*Values are median (range). †Exploratory laparotomy in one patient, bypass in one, palliative resection in one and non-curative resection in three patients.

Table 3 Pathological findings in resected patients

	No. of patients (n = 47)
Depth of tumour invasion	
T1	3
T2	18
T3	19
T4	6
Unknown	1*
JGCA, nodal status	
N0	1
N1	7
N2	9
N3	30
JGCA, pathological response	
Grade 0	6
Grade 1a	33
Grade 1b	2
Grade 2	5
Grade 3	1

*Not evaluable as no residual cancer cells. JGCA, Japanese Gastric Cancer Association.

Surgical findings and surgical pathology

Forty-nine patients proceeded to surgerv (*Table 2*). Resection with curative intent was undertaken in 46 patients. One patient had only exploratory laparotomy because of peritoneal metastases, one underwent gastrojejunostomy, and one required palliative resection to stop bleeding from the primary tumour. Of the 46 patients who had resection with curative intent, R0 resection was performed in 36, R1 in four (positive surgical margin, three; positive peritoneal cytology, one) and R2 in six with unresectable tumours (*Table 3*). Thus, the proportion of R0 resections in the 55 eligible patients was 65 (95 per cent c.i. 51 to 78) per cent.

The pathological response rate in resected patients was 15 (95 per cent c.i. 7 to 27) per cent.

Adverse events from chemotherapy

Toxicity of grade 3 or above included leucopenia (31 per cent), neutropenia (55 per cent), anaemia (24 per cent), febrile neutropenia (16 per cent), nausea (36 per cent), vomiting (13 per cent) and diarrhoea (5 per cent). Two patients died from myelosuppression after the initial chemotherapy course, giving a chemotherapy-related mortality rate of 4 per cent (two of 55 patients).

Surgical complications

Surgical complications are shown in *Table 4*. One (2 per cent) of 49 patients died from multiple organ failure 3 days after thoracoabdominal surgery for oesophageal invasion in addition to a total gastrectomy with pancreaticosplenectomy.

Overall survival

The 3-year survival rate was 27 (95 per cent c.i. 15 to 39) per cent, and thus the lower limit of the 95 per cent c.i. was higher than the prespecified threshold (*Fig. 4*). Median survival was 14·6 (95 per cent c.i. 10·1 to 24·1) months.

Table 4 Surgical complications in the 49 operated patients

	No. of patients
Leakage	1 (2)
Pancreatic fistula	6 (12)
Abdominal abscess	2 (4)
Pneumonia	2 (4)
Ileus	0 (0)
Wound infection	2 (4)
Stenosis of anastomosis	1 (2)
Cardiac failure	1 (2)
Renal dysfunction	1 (2)
Other	6 (12)

Values in parentheses are percentages.

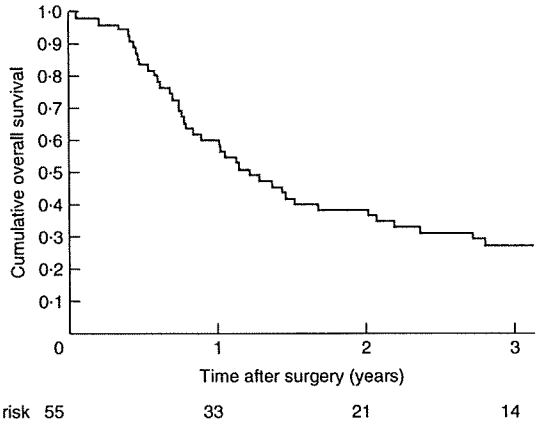

Fig. 4 Kaplan–Meier overall survival curve for the 55 eligible patients

Discussion

This multi-institutional phase II prospective trial of neoadjuvant chemotherapy in locally advanced gastric cancer with extensive lymph node metastases showed that multimodality treatment can achieve a high 3-year survival rate of 27 per cent. Usually these patients rarely survive for more than 3 years when treated by chemotherapy alone or by surgery followed by postoperative chemotherapy. Thus, the protocol treatment was effective for these patients, but was achieved at the cost of considerable morbidity and mortality, and the study had to be stopped prematurely because of treatment-related deaths.

The combination chemotherapy of irinotecan plus cisplatin was chosen because it had achieved a high response rate of 59 per cent in a previous phase II study of chemotherapy-naive patients with metastatic gastric cancer[11]. At the start of the present study in 2000, this was considered to be the most effective and promising regimen for gastric cancer. In Japan, based on these data, a phase III trial was initiated to determine the superiority of irinotecan plus cisplatin compared with 5-fluorouracil (5-FU) alone for metastatic gastric cancer[17]. In the present study, the clinical response to preoperative chemotherapy was 55 per cent, comparable with previous results using this regimen in patients with metastatic gastric cancer[11]. Although the above-mentioned Japanese phase III trial (JCOG 9912) did not demonstrate superiority for this regimen compared with 5-FU alone, a subset analysis for tumours with target lesion defined by RECIST

showed that combination chemotherapy of irinotecan plus cisplatin gave a median survival of 12·1 months, which was significantly longer than for 5-FU alone[17]. This suggested that irinotecan plus cisplatin was especially active against tumours forming bulky masses[17]. In contrast to the impressive clinical response of metastatic nodes, the pathological response in the primary tumours was relatively low in the present study. In gastric cancer, the pathological response rate is usually less than 20 per cent for any chemotherapeutic regimen, suggesting the importance of appropriate local control by surgery. The relatively good overall survival at 3 years in the present study appears to be due to the effects of neoadjuvant chemotherapy in two ways: downstaging of lymph node metastases, which enabled R0 resection in 65 per cent of patients, and good control of micrometastases.

Treatment-related death was observed in 5 per cent of patients in this study, indicating that this treatment protocol is hazardous. Of three patients, two died from chemotherapy-induced myelosuppression. Neutropenia and diarrhoea were the major toxicities of this regimen, as reported previously[11,17]. Compared with these trials, toxicity in the present study was relatively low, but the mortality rate was high. In two treatment-related deaths from chemotherapy, severe myelosuppression appeared immediately after the first administration of irinotecan plus cisplatin. Boku and colleagues[17] observed severe diarrhoea only during the first course of the same regimen in patients with unresectable gastric cancer. Noda and co-workers[18] reported on the efficacy of combination therapy with irinotecan plus cisplatin for small cell lung cancer, using a different schedule and dosage than those in the present study. They observed treatment-related deaths in three patients (4 per cent) during the first or second cycle of chemotherapy. Taken together, all of these results indicate that severe haematological toxicity and diarrhoea should be managed carefully, especially during the initial cycles of chemotherapy.

Recently, genetic polymorphism of UTG1A1, which is involved in glucuronidation of SN-38 or is an active metabolite of irinotecan, has been reported to be associated with irinotecan toxicity[19,20]. Polymorphisms of UGT have also recently been suggested as a risk factor for irinotecan-induced neutropenia[21]. These factors might have been involved in the treatment-related deaths observed in the present study, although genetic analysis was not performed. Patient risk may be reduced not only by careful management of myelosuppression, but possibly also by patient selection based on genetic analysis. However, further studies are needed to confirm this. Because the combination chemotherapy regimen employed in this study is difficult to manage in terms of toxicity, a new phase II study has been initiated to evaluate a preoperative S-1 (oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine and potassium oxonate) plus cisplatin regimen, which is considered less toxic for patients with extensive nodal metastases. S-1 and cisplatin showed a high response rate of over 50 per cent with mild toxicity in recent trials of patients with metastatic gastric cancer[22,23].

The operative mortality rate in this study was 2 per cent. In the JCOG 9501 trial, which compared D2 with D2 plus para-aortic nodal dissection, the mortality rate was 0·8 per cent for D2 plus para-aortic nodal dissection[13], whereas in the JCOG 9502 trial, which compared an abdominal approach with a left thoracoabdominal approach for gastric tumours invading the oesophagus, mortality rates were 0 and 4 per cent respectively[24]. Thus, the thoracoabdominal approach was the more hazardous of the two procedures. Because the influence of preoperative chemotherapy on surgery is unclear, patients who require such an extensive thoracoabdominal operation should probably be excluded from future studies.

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The authors declare no conflict of interest.

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