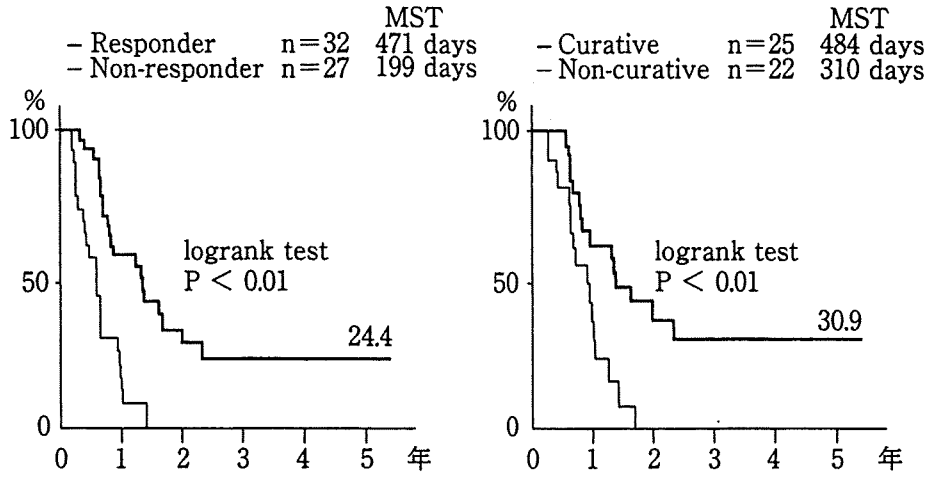


図 4　SURVIVAL

BSA	TS-1 administration
<1.25 m²	80 mg/day
1.25 m²～1.5 m²	100 mg/day
more than 1.5 m²	120 mg/day

図 5　TS-1 + CDDP Therapy

表 10　Response

	No of cases	CR	PR	NC	PD	RR (%)
overall	120	1	74	42	3	62.5
primary	120	2	72	45	1	61.7
metastatic focus						
LN	74	4	52	18	0	75.7
liver	7	1	1	5	0	28.6
peritoneum	*21	0	5	14	2	23.8
others	**4	0	0	3	1	0.0

**lung and pleura, ovaryx3

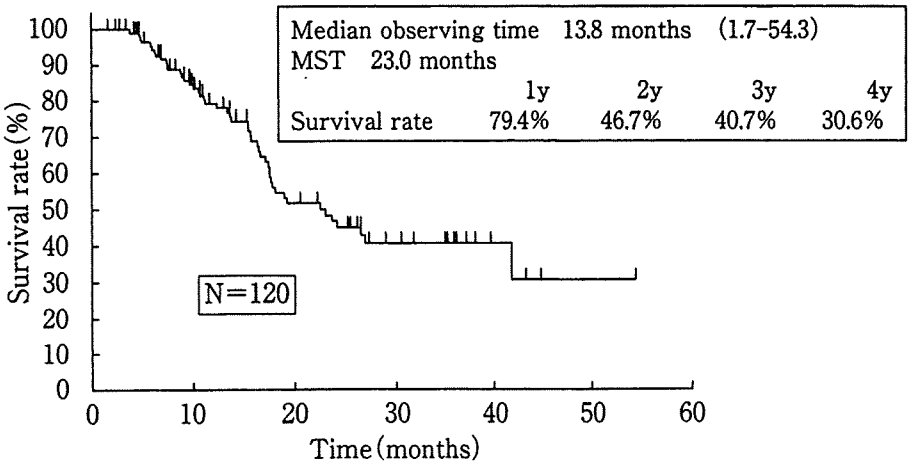


図 6　Overall Survival

表 11　MULTIVARIATE ANALYSIS — Cox Proportional Hazard Model —

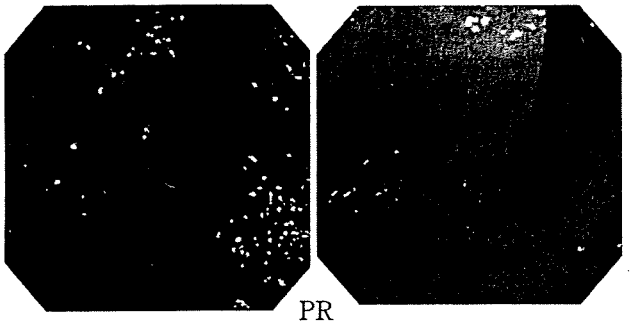
Variables	Hazard ratio	95% confidence limits	*P*-value
fH (0 / 1)	6.308	(2.145-18.553)	0.0008
Curability (A,B / C)	3.608	(1.610-8.085)	0.0018
PS (0 / 1,2)	2.856	(1.308-6.234)	0.0084
Response (CR,PR / NC,PD)	2.585	(1.155-5.787)	0.0209

Resected cases N=93　　SAS Ver.8.2, Score method

表 12　術後合併症

	延べ例数
膵炎	7
イレウス	3
縫合不全	2
腹腔内膿瘍	1
肺炎	1
MRSA 創感染	1
膀胱炎	1
帯状疱疹	1
出血性 shock	1

術後合併症発生率 13.3%

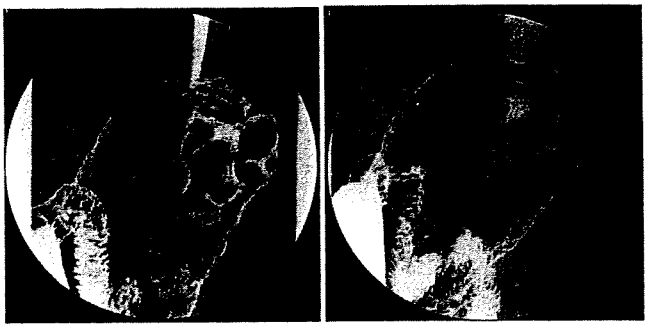


Before　PR →　After 3 courses

図 8　Endoscopy

効例では，腫瘍があった場所が退縮して浮腫になってくることで，切除ラインがわかりやすいことを経験しています。1カ月以上間隔を空けると，浮腫になっていた場所が線維化して，剥離がしにくくなります。

ビデオにて症例を供覧します。67歳女性です。Fornix にかなり大きな2型の腫瘍があります。3クール施行して，縮小率 37.5%ということで，かなり縮小していることがわかります(図7)。内視鏡像では，クレーターが浅くなって，周堤が低くなっています（図8)。



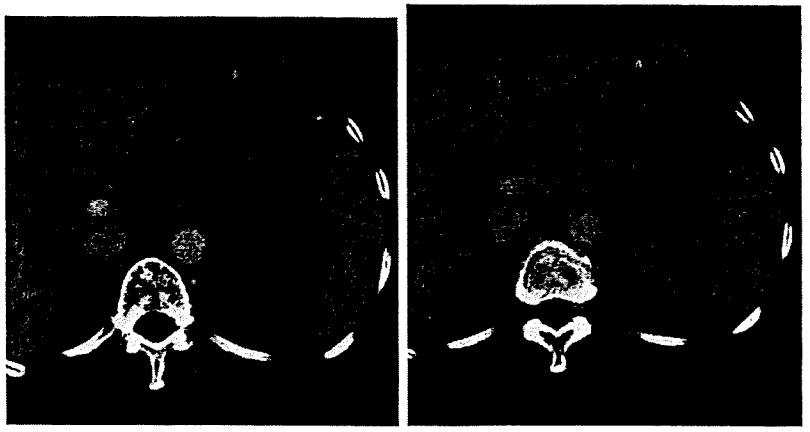
Before　After 3 courses
37.5%縮小
IR

図 7　Upper GI series

CT では，原発巣にリンパ節も巻き込まれており，直接脾門部に侵潤しているかなり大きな腫瘍があります（図9)。NAC 後は 81.8%の縮小で，非常によく効いたと思います。脾門部の腫瘍が縮小しているのがわかります。

まず，右の胃大網静脈の操作ですが，この症例はよく効いたということもありますが，剥離ラインがわかりやすくなっていました。しかし，操作するたびに oozing といいますか，どこから出てくるかわからないような，じわっと浮いてくるような出血が常にあるというのが化学療法後の特徴かと思います。

次に小彎側に移って，右の胃動脈の周囲です。胃の手術では，主要の血管は二重結紮ならびに刺入結紮を原則にしてやっています。今 No.12a



Before　　After 3 courses

81.8%縮小
PR

図 9　Abdominal CT

の郭清を追加しているところです。とくにそれほど血管を痛めたわけではないのですが，oozingが非常に多いので，リンパ管や血管の多いところはできるだけ結紮していくという方針にしています。当院では電気メスを多用しますが，LCSも使用します。

No.9リンパ節からNo.11リンパ節のほうに向かって郭清しますが，郭清するラインが非常にわかりやすくなっています。2群以上のリンパ節はできるだけ術中に分けておき，できるだけ正確に分類できるようにしています。

これは左の胃静脈を結紮するところです。先ほどのビデオですと，LigaSure AtlasやLCSで処理できるのかもしれません。

2群のリンパ節を持ち上げながら，左動脈の周囲を郭清します。このように脈管をしっかり出して処理するのがもっとも安全かと思います。このような操作をするだけでもoozingが起きています。

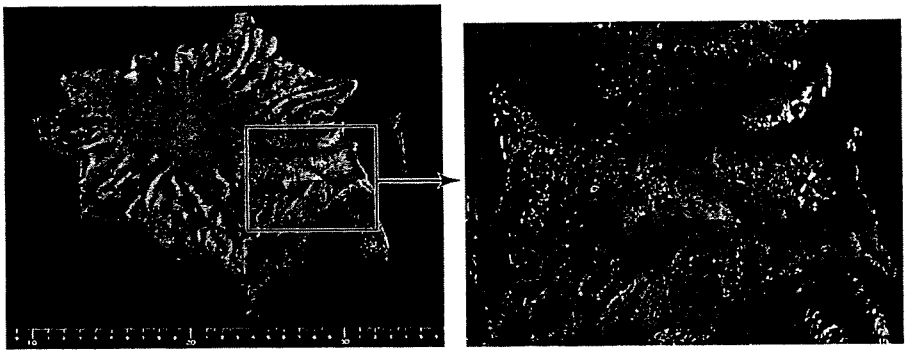
膵臓の尾部と脾臓の脾門部と原発巣が一塊になっていて剝離できないのがわかりまして，この段階でPSTに術式を変更しました。No.11リンパ節のほうの追加郭清を行います。常にこのように濡れている視野になってしまい，なかなかdry fieldにならないのが化療後の特徴かと思います。

横隔膜脚の手前からNo.11リンパ節にかけての組織を取っていますが，ここには転移がなかったと思います。脾動脈にテーピングして，これを切離します。これも二重結紮しますが，必ず太い血管を刺入結紮しています。

あとは細かな血管を処理してから膵臓を切ります。残るほうは長鉗子ではさみます。膵は一気に切ってしまい，膵管を処理してfish mouthに閉じるというやり方です。取った後で少し追加郭清しています。この症例はその後No.16リンパ節も郭清しています。

これが取った胃です（**図10**）。原発巣自体はかなりよく効いており，クレーターがはっきりわからなくなっているという状況でした。最終的には3型の48 mm×40 mmの腫瘍で，他臓器に直接浸潤しており，リンパ節転移は組織学的には3個でしたが，他の計6個には化療前には転移があったような名残があったということです。進行度はIVです。手術時間は，ビデオを撮ったこともあるのですが，4時間40分で，出血量860 m*l*，術後16日目に退院になっています。

2例目は58歳男性です。タール便で発症して，ヘモグロビンが7.3/d*l*まで下がりました。前庭



Type 3, 48×40 mm, por1 with lymphoid stroma, SI (spleen), N2 (3/63), H0, P0, CY0, ly3, v2, PM-, DM-, Stage IIIB, Curative B
Histological effect of chemotherapy : Grade 1a
Fibrosis without viable cancer cells : No.1 (2/2), No.2 (3/5), No,4sa (1/1)

図 10　Operative procedure and resected specimen

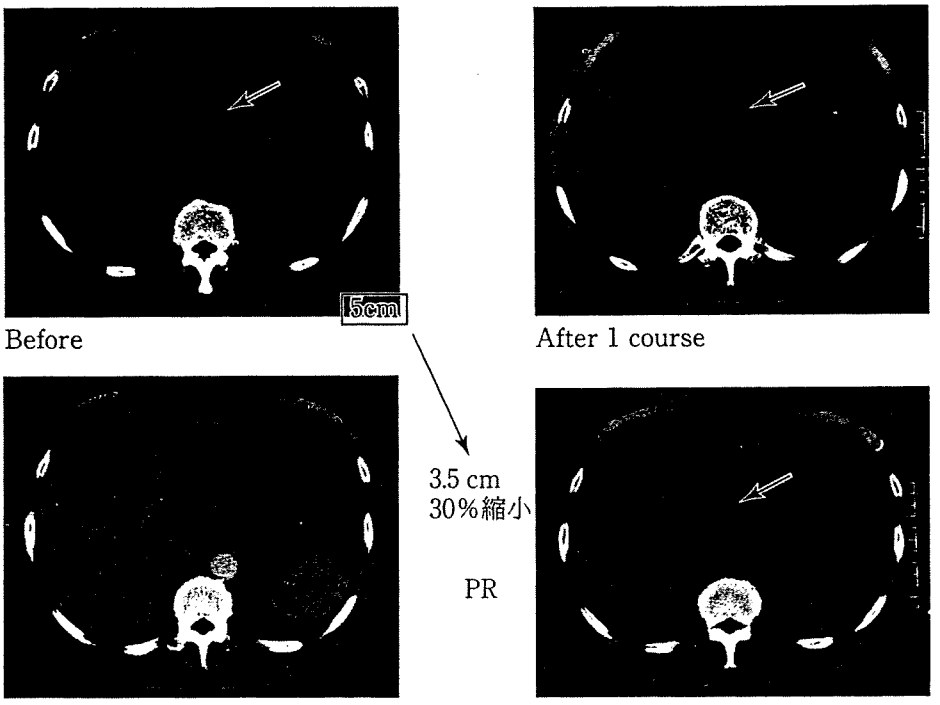


図 11　CT による bulky N2 の評価

部に少し狭窄があるということでした。これはなかなか判定が難しいのですが，33%の縮小でした。2コース後，staging laparoscopy (SL) を施行して，PとCYがないことを確認し，進行度IIIということでした。ただ，bulky N2がありまして，5 cm大の腫瘍があります（図11)。この範囲がはっきりしないのですが，2コース後に2個に離れるのではないかと思わせるような間隔が空いてきました。

ここに原発巣があって，SEであることはSLで確認しています。問題はここのbulky N2をいかにして取るかということです。

今回は，先に胃切除をしてから，腫れているリンパ節を取りに行くという方針にしました。

左の胃動脈を切って胃を上に翻転し，視野をしっかり取りました。この段階ではリンパ節が郭清できるかどうかわかっていません。実際に触ってみますと，動かなくて，この後どうなるか，まだ先がよく見えていない状況です。肝動脈との境界はなんとか剝がれるだろうと予測しています。膵臓のところは，手で持って，なんとかいけそうだという当たりを付けます。次の段階になると何とかなるだろうという状況に入ってきています。

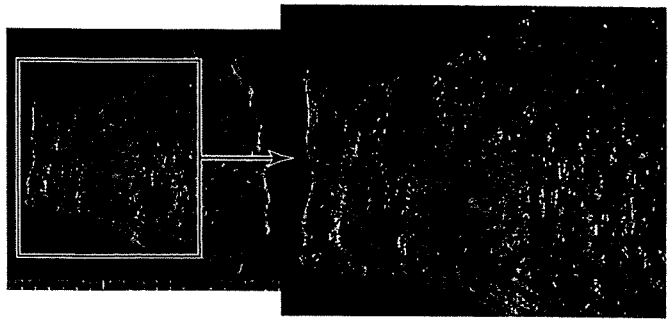
ここで膵臓からの出血がありました。視野が悪く，勢いを止めるためにまず針糸をかけています。少し勢いが弱まって，部位が確定してきましたので，そこに対して刺入結紮をかけています。総肝動脈はわかったのですが，固有肝動脈がよくわかりませんでした。テーピングして引っ張ってみて初めてオリエンテーションがつきました。誤って固有肝動脈を切ると，後で血管吻合ということになります。こういう症例で外膜まで血管をきれいに出すというのは難しいと思います。*en bloc* という考え方は大事ですが，とにかくまず main tumor を取って，あとで追加郭清するという方法でもいいかと思います。

ここまで来ますと，切除できるということは手の内に入っています。できるだけ出血させないようにして操作を続けます。術後は合併症が怖いですから，残るほうはしっかり結紮していくという考え方です。

総肝動脈に沿うようにリンパ管が存在します。この症例だけでなく必ず存在するのですが，この症例は非常に太くなっています。これはやはり転移のせいかと思います。

ここで腫大したリンパ節を切除してしまいます。これで bulky N2 が取れました。この操作を終えて，あとは No.12〜13 リンパ節を（普通はここをひっくり返して小彎側に持ってくるのですが）右側から取っています。

ここには転移がないと予想しています。この症例も No.16 リンパ節を郭清したのですが，時間がかかるので郭清した後の視野だけお見せします。4 領域を郭清しています。



手術時間 5 時間，出血量 780 m*l*，術後第 15 日目に退院する。

図 12　切除標本所見

type 3（50×48 mm），tub2，SE，N2（6/65），ly3，v3，H0，P0，CY0

切除標本です（**図 12**）。3 型で，化療がそれなりに効いているという肉眼形態を示しています。SE でリンパ節転移は 6 個でした。Stage III B，手術時間は 5 時間で，出血量 780 m*l*，術後第 15 病日に退院しています。

術前化学療法の易出血性については，抗癌剤が血管にダメージを与えるのではないかと考えています。血管が非常にもろくなるようです。損傷時，とにかく慌てずに，まずは押さえることだと思います。圧迫する！それから勢いを止めるという時間稼ぎもあります。その間に，視野が狭いといろいろとトラブルになりますので，視野を広げていき，血管がしっかり同定できたら，それを剝離してテーピングする。いろいろな血管鉗子から合うものを選んでいくということです。

私どものところでは大動脈周囲の郭清を約 800 例に施行してきましたが，1 例だけ大出血を来したことがあります。このときはさすがに手に負えなくて圧迫だけし，血管外科の先生を呼んで操作をしていただきました。

また血管は合併切除しなければならないこともありますので，門脈再建法をお見せします。当院は 5-0 のモノフィラメントを使い，1 本で連続縫合にて施行します。まず前壁を連続縫合し，それをひっくり返して後壁を縫合して終了です。

血管吻合に関しては3点支持にしたりいろいろなやり方があり，血管外科の専門の先生にお願いしたほうがいいかと思います。ただ，血管を処理できるとかなり切除率が上がることもありますし，自信がついて操作するときにどんどん進んでいけるということもありますので，ある程度は血管を処理できる能力を持っていたほうがいいと思います。また，すぐに血管外科の先生が来るとも限りませんので，ある程度のトレーニングをしておく必要があると思っています。

前壁が終わったら，ひっくり返して針を通して，今度は後壁の連続縫合です。こういう操作は肝・胆道をやる先生はよくされると思います。手技もそうですが，慣れというのは大事だと思います。

これは門脈，上腸間膜静脈（SMV）と脾静脈に血管鉗子をかけて，その枝にもクランプしてあります。

これで吻合が終わりまして，クランプを外して少し出血させてから閉めます。

注意事項としては，胃癌に対するNAC後の手術ということで，基本的なことですが，解剖を熟知する，病的な剝離や本来ないような浸潤からの撤退などです。本来ないような癒着剝離がありますので，オリエンテーションをしっかりつけるということです。

それから良い剝離層を見つけること。NACが非常によく効いている症例に関しては操作がしやすいということがあります。できるだけドライフィールドにするということです。

それから，いろいろな最新器具を使っています。結紮を多用するということと，剝離がよくわからないところは，注射器で癒着部に生食を注入して，間隔をとって剝離するということもします。それから，できるだけ不要な剝離はしないことだと思います。

まとめです。NACによって奏効例や治癒切除が施行できた高度進行胃癌では遠隔成績の改善が期待されます。また，NAC後の手術操作は易出血性でやりにくいところがありますが，剝離，切離，止血の技術を十分に駆使して，ていねいな手術を心掛けることによって乗り切ることができます。血管損傷時に備えて血管縫合の技術を身に付けたいと思います。

外科医は不測の場合に遭遇しても冷静に対応し，毅然とした態度で事態に対応できるように，普段から訓練しておくことが望ましいと考えます。

ディスカッション

宇田川（司会）　いろいろな要素が含まれていたと思いますが，どなたかご発言，ご質問ございますか。

臼杵尚志（香川大学手術部）　おっしゃるように化学療法後というのは出血しやすくて，それとよく問題になるのが，膵臓に浸潤しているかどうかギリギリのところで，いつもヒヤヒヤしながら剝離しています。そういった際に，膵の表面から出血して縫ったところから後で膵液が少し漏れることがあるのですが，膵液漏に対して心掛けておられることがありましたら教えていただきたいと思います。

梨本　実は先輩の先生には怒られるのですが，私達は膵炎が非常に多く，30％くらいありました。それで反省して一つ一つ変えていったのですが，合併切除するときは仕方ないのですが，膵皮膜をあまり剝かないようにするというのが一つあります。それから，損傷した場所をそのときに補強する。あとでしようとすると必ず忘れますので，そのときにする。

そして膵臓に浸潤しているかという問題があります。膵臓に切り込むようなかたちで剝離を進めていきますと，取れるときと取れないときが大体わかります。浸潤していればPSTにすることもあります。例えばNo.8Pリンパ節のほうからずっと後腹膜に浸潤しているようなものは取れないと思いますし，触っても取れないと思いますので，そのへんは操作しながら大体判断がつくかと思います。

臼杵　ギリギリで削り取ったような場合に，何か処置はされていますか。

梨本　私はそこにサージセル綿を置くのは好

きなのですが，断端は必ず縫います。縫っておいて，その上に当てるようなことはしていますし，ドレーンがその近くに行くようにしています。それから，膵酵素の抑制剤を使います。普通のことしかしておりません。

宇田川（司会）　先生は合併症で膵炎が多いという数字を言われていましたが，あの膵炎は膵液漏や膵損傷との絡みのものでしょうか。

梨本　そういうことです。今のCTC AE ver. 3.0の診断基準で言うとGrade 2以上のものを言っています。Grade 1まで入れると非常に高くなって，半分以上になってしまいますので，内科的な処置を必要とするGrade 2以上の合併症だけを取っています。

宇田川（司会）　全体的な膵炎，いわゆる内科的な膵炎とは違うのでしょうか。

梨本　全体的な膵炎というよりも，いわゆる局所的な膵液漏です。

石井正紀（東海大学外科）　術前化学療法ということで，効く症例に対しては，どういったところで次は手術に行くと決めるのでしょうか。それから，効かないときの「じゃあ手術をしよう」という判断はどういうかたちでされているでしょうか。

梨本　NACは原則的には2クールだと思っています。ただ，例えばCYがあったりPがあったり，いろいろな状況があって，すべて根治的に取れる症例だけを最初から行っているわけではありませんでした。しかし，原則は2クールです。始めるときに「最低2クールはしましょう」という話をしています。2クール終わった後に，手術するか3クール目に行くかは，その段階でまた説明します。ということで，話し合いながら進めて行きますが，大体患者さんは「先生にお任せします」と言われます。私達の感覚では，すごくよく効いている症例は3クール目まで行ってもいい。ただ，3クール目まで行きますと，効いてしまった組織がだんだん治ってきて，線維組織になって，剝離しにくくなるということを経験していますので，私は原則は2クールだと思っています。

それから，効く症例のうち，1クールをやって効く率は6割くらいだと言われています。ですから，4割くらいは1クールやってもなかなか変化がわからないということなので，最低限2クールは行いたい。ただ，PDになるような症例に関しては1クールでやめていいと思っています。

石井　手術手技なのでお伺いしようか迷っていたのですが，適応はどのように引いておられますか。

梨本　適応は，T3以上でN2以上と決めています。

石井　例えば，明らかな非治癒因子がある場合に，普通に手術ができて，非治癒因子が今回手術すればちゃんと取れそうだというものと，どう考えても最初の非治癒因子は普通に手術しても残るという場合がありますね。そのへんは手術に…。

梨本　まず，curativeに取れそうな場合です。

例えばbulky N2でやれば取れるという感じなのですが，切除しても今までのデータでは予後が悪いのです。当院のエビデンスをベースにして，T3，N2以上の症例ということでやっていますが，それはケースバイケースです。できるだけSLを施行するようにして，Pのファクターを把握するようにしています。

それから，非治癒切除例に関しては当然化学療法をするのですが，これは最終的に手術しない症例もたくさんあって，4型のP3に関しては手術しないという方針にしています。

宇田川（司会）　ありがとうございました。次に進ませていただきます。

●症 例●

S-1/CDDP療法による術前化学療法が著効し根治手術が得られた進行胃癌の1例

松井 恒志[*1] 梨本 篤[*1] 中川 悟[*1] 野村 達也[*1] 藪崎 裕[*1]
瀧井 康公[*1] 土屋 嘉昭[*1] 田中 乙雄[*1] 太田 玉紀[*2]

[*Jpn J Cancer Chemother* 35(3): 499-501, *March*, 2008]

A Case of Advanced Gastric Cancer Responding to Neoadjuvant S-1/CDDP Therapy: Koshi Matsui[*1], Atsushi Nashimoto[*1], Satoru Nakagawa[*1], Tatsuya Nomura[*1], Hiroshi Yabusaki[*1], Yasumasa Takii[*1], Yoshiaki Tsuchiya[*1], Otsuo Tanaka[*1] and Tamaki Ohta[*2] ([*1]*Dept. of Surgery*, [*2]*Dept. of Pathology*, *Niigata Cancer Center Hospital*)

Summary

A 77-year-old male had complaints of epigastralgia. Gastrointestinal endoscopic examination revealed type 2 advanced gastric cancer. Computed tomography revealed metastatic Bulkey group 2 lymph nodes. The diagnosis was sStage ⅢB gastric cancer (sT3 sN2 sH0 sP0 CY0) at staging laparoscopy. S-1 (100 mg/body/day) was orally administered for 3 weeks followed by a drug-free 2 weeks, and CDDP (74 mg/body/day) was given intravenously on day 8. After 3 courses of chemotherapy, the primary lesion and the regional lymph nodes were significantly reduced in size. He was judged as clinical PR, followed by total gastrectomy, splenectomy and lymph node dissection. The pathological findings showed that there were very few cancer cells in the primary lesion, and lymph nodes had become scarred and fibrous. The final diagnosis was T2 N0 H0 P0, fStage ⅠB and curability A. Key words: Gastric cancer, NAC (*Received Jul. 9, 2007/Accepted Aug. 30, 2007*)

要旨 症例は77歳，男性。心窩部痛を主訴に上部消化管内視鏡検査を施行したところ，胃体上部大弯から前壁に及ぶ2型胃癌（por 1，por 2）を認めた。腹部造影CT検査にて胃小弯側にBulkey N2のリンパ節腫大を認め，診断的腹腔鏡検査にてsT3 sN2 sH0 sP0 CY0，sStage ⅢBと診断。術前化学療法の方針とし，S-1 100 mg/body/dayを3週投与2週休薬，day 8にCDDP 74 mg/body/day点滴静注を1クールとしたレジメンで3クール施行。化学療法後，原発巣の縮小およびリンパ節腫大の縮小を認め，PRと判定した後，脾合併胃全摘術，D2リンパ節郭清を施行した。病理組織学的検査では原発巣にごく少量の癌細胞の遺残（30 μm）を認めるのみで，リンパ節転移は認めなかった。最終的にStageは，T2 N0 H0 P0, fStage ⅠBでdown-stagingしており根治度Aであった。術後の経過は順調で現在外来通院中である。

はじめに

根治手術が困難な進行胃癌症例の治療成績は悪く，これらの症例に対する標準的な治療はいまだ検討中である。現在われわれは，根治手術が困難と思われる高度進行胃癌症例に対し，積極的に術前化学療法（neoadjuvant chemotherapy: NAC）を行っている。今回われわれは，腹腔動脈を取り巻くリンパ節が一塊となって腫瘤を形成するBulkey N2転移を伴う進行胃癌に対し，NACを施行後，原発巣とリンパ節腫大の著明な縮小が得られ脾合併胃全摘術を施行し，根治度Aが得られた1例を経験したので報告する。

I．症 例

患者: 77歳，男性。

主訴: 心窩部痛。

家族歴: 特記すべきことなし。

既往歴: 高血圧。

現病歴: 2006年10月より心窩部痛が出現。近医を受診し，上部消化管内視鏡検査にて胃体上部大弯に2型の

[*2] 新潟県立がんセンター新潟病院・病理部

連絡先: 〒951-8566 新潟市川岸町2-15-3 [*1] 新潟県立がんセンター新潟病院・外科
松井 恒志

0385-0684/08/¥500/論文/JCLS

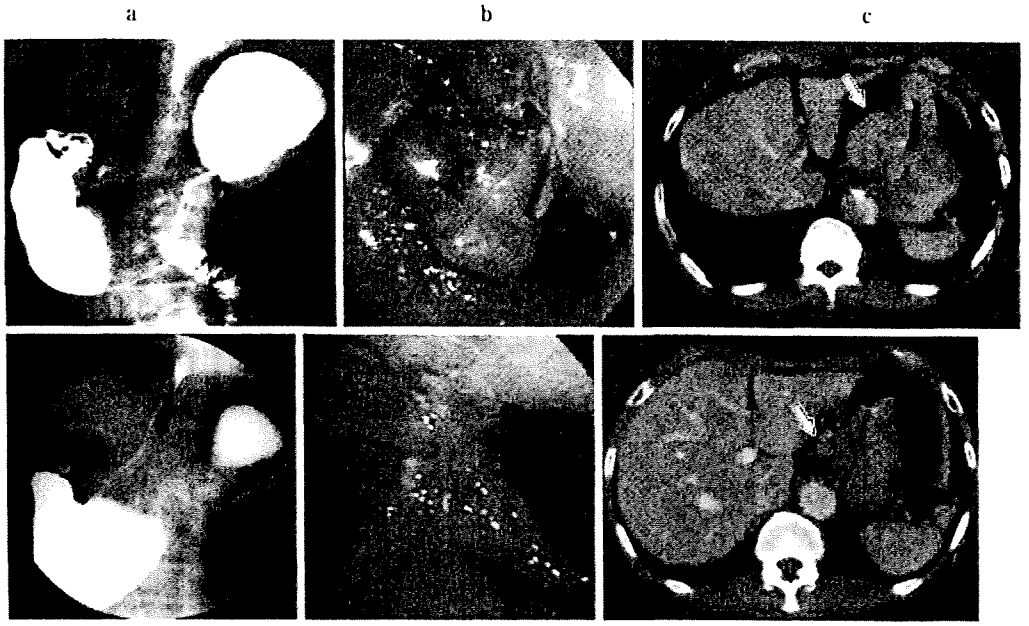


図 1 上部消化管造影（a, d），上部消化管内視鏡（b, e），腹部造影 CT（c, f）
a, b, c: 化学療法前，d, e, f: 化学療法後。

腫瘍を認め，生検検査にて低分化腺癌と診断．12月に当科紹介．

初診時現症: 身長 160.5 cm，体重 48.3 kg，体表面積 1.48 m²，貧血，黄疸なし．腹部は平坦・軟で圧痛なし．

血液生化学検査: Hb 11.8 g/dL と軽度の貧血を認めた以外は，特記すべき所見を認めなかった．腫瘍マーカーは CEA，CA19-9，CA125 すべて正常範囲内であった．

上部消化管造影検査: 胃体中部大弯を中心とした隆起性病変を認め，全周性に壁硬化による狭窄像を認めた（図 1a）．

上部消化管内視鏡検査: 胃体中部大弯に 2 型の腫瘍を認め，生検検査にて por 1，por 2 と診断（図 1b）．

腹部造影 CT 検査: 胃体部小弯側の著明なリンパ節腫大があり，胃大弯側後壁に著明な壁肥厚を認めた（図 1c）．

経過: 診断的腹腔鏡検査を施行し，sT3 sN2 sH0 sP0 cY0，sStage ⅢB と診断し，NAC の方針とした．レジメンは S-1 100 mg/body/day を 3 週投与 2 週休薬，day 8 に CDDP 74 mg/body/day の点滴静注を 1 クールとし計 3 クール施行した．副作用は NCI-CTC 判定基準に基づき，grade 1 の発熱と色素沈着を認めるのみであった．

効果判定: 上部消化管内視鏡検査では，病変の著明な縮小と周堤の平低化を認めた（図 1e）．上部消化管造影検査においても隆起の平低化を認め，狭窄も改善していた（図 1d）．腹部造影 CT 検査では，胃壁の肥厚が縮小し病変部は不明瞭化した．また，胃体部小弯のリンパ節腫大は 1 クール後に約 60%縮小し，3 クール後には 18×10 mm 大と縮小が維持されていた（図 1f）．以上より，化学療法の効果を RECIST に準じ PR と判定．休薬 3 週間後に手術を施行した．

手術所見: 腫瘍は，胃体上部大弯から前壁に認め T3（SE）と判断．胃周囲のリンパ節が硬く触知され，手術は脾合併胃全摘術，D2 郭清，Roux-en Y 吻合にて再建した．摘出標本の肉眼所見では，4.0×3.0 cm 大の 3 型の腫瘍でリンパ節は 1 群に腫大を認め，sT3 sN1 sH0 sP0 sCY0, sStage ⅢA，根治度 B と診断した（図 2a）．

病理組織学的検査: 原発巣の腫瘍は，ごく少量の癌細胞の遺残を認めるのみ（30 μm²）で（図 2b），por 2，sci，pSS，INFγ，ly0，v0．リンパ節転移は認めず（0/41），化学療法の効果によると思われる線維化したリンパ節を 10 個認めた．癌細胞は空胞化し，核濃縮がみられた（図 2c）．最終的には NAC 後の Stage は，T2 N0 H0 P0，fStage ⅠB で根治度 A であった．

術後経過: 術後経過は良好で第 11 病日退院となり，現在再発所見なく外来通院中である．

Ⅱ．考　察

Bulkey N2 転移陽性胃癌は，たとえ切除し得ても微小遠隔転移が高頻度であり，その治療成績は極めて不良である[1,2]．広範囲にリンパ節転移を認める症例において，根治度 B の手術が可能であっても，すでに微小遠隔転移を伴っていることが多く予後は不良であり，手術による治療の限界と思われる．そこで，進行胃癌に対する化学療法として S-1/CDDP 療法は高い奏効率が得られ，ま

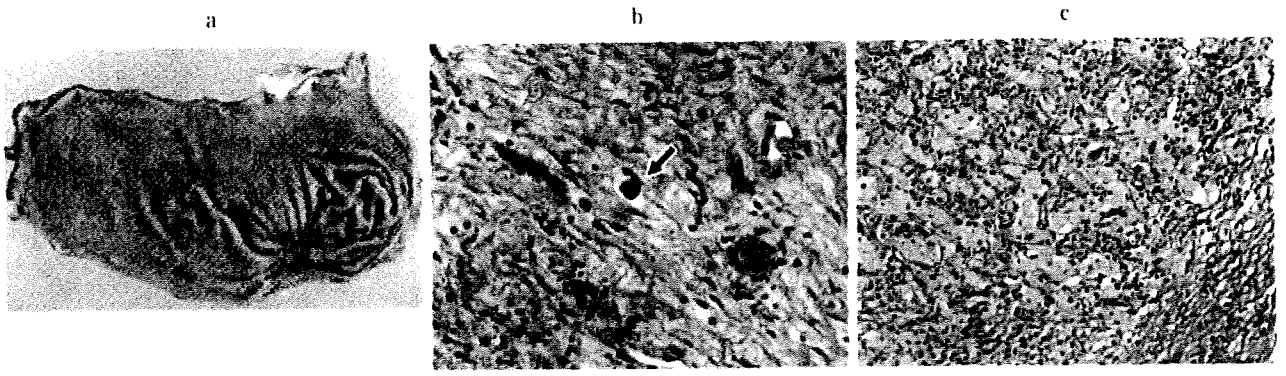


図 2
a: 摘出標本，b: 原発巣（HE×40・原倍率），c: 摘出リンパ節（HE×20・原倍率）

たNACとしての有用性も多く報告されている[3]．以前NACとしてS-1/CDDP療法を行い，病理学的にCRが得られた症例を報告したが[4]，組織学的効果判定でGrade 3となる症例は非常にまれである．本症例は5 cm以上あった2型胃癌がNACにより縮小し，深達度が漿膜下にまで及んでいるにもかかわらず，ごく少量の癌細胞の遺残を認めるのみであった．また，NACの効果と思われる線維化したリンパ節を多数認め，リンパ節に悪性細胞を認めなかった．化学療法による効果の経過は，1クール終了時点で腹部造影CT上，胃壁の肥厚はほぼ改善しており，リンパ節腫大も約60%まで縮小していた．しかし2クール目以降は，リンパ節に関してはわずかな縮小のみであった．それに対して上部消化管造影および上部内視鏡検査では，化学療法を重ねるごとに腫瘍が縮小した．リンパ節に関してはかなり早い段階で化学療法が奏効しているが，原発腫瘍に関しては徐々に効果がみられている．これは癌細胞量の違いが関係しているのではないかと思われるが，原発巣やリンパ節腫大の大きさが化学療法の投与回数や投与量の決定に関連するのではないかと考えられる．つまり縮小効果があれば，より癌細胞量が多い部分に関してはさらなる抗癌剤の投与により効果が期待できる．あくまで予想ではあるが，もう1クール追加していれば病理学的CRとなった可能性が非常に高かった症例と思われた．

当科では，進行胃癌に対するNACとして経口摂取が可能であればS-1/CDDP療法を，経口摂取不可能であればpaclitaxel/5-FU/CDDP療法としている[5]．以前，P0CY1の胃癌に対してNACによるCYの陰性化が高率で根治切除率を上昇させると報告した[6]．しかしながら，予後の改善までに至っているとはいい難いのが現状である．本症例のように，CY陰性で治癒切除も可能と思われる症例でのNACの意義について議論があると思われるが，当科では現在，高度なリンパ節腫大を認める症例や腹膜播種が疑われる症例では，積極的に診断的腹腔鏡検査を施行している．CY陽性症例では腹腔内投与のためのポートを留置し，抗癌剤の腹腔内投与も行っている．抗癌剤の副作用として食欲不振や骨髄抑制などに注意が必要であるが，S-1/CDDP療法は比較的副作用も強くなく外来投与が可能であり，患者のQOLを阻害することは少ない．当科では原則2クールの投与とし，投与後3週間で手術としている[8]．しかし本症例のように，NACが著効した症例では副作用が軽微で継続可能であれば，患者と相談し3クール目を施行する場合もある．NACの生存期間の延長への寄与はいまだエビデンスがないのが現状であるが，今のところは潜在的微小転移巣に対する治療，あるいはdown-stagingを図り，生存期間の改善および治癒率の向上が主な目的である．そのため，NACの施行回数や手術時期に関してNAC症例を蓄積し，レジメンを検討していくべきだと思われる．

文　献

1) Sasako M: Surgical management of gastric cancer: the Japanese experience. (Eds by Daly JM, *et al*), Management of Upper Gastrointestinal Cancer, WB Saunders, London, 1999, pp107-122.
2) 久保義郎，栗田　啓，石崎雅浩・他：2群リンパ節転移陽性胃癌の治療方針．日臨外会誌　63(3)：550-555，2002.
3) Koizumi W, Tanabe S, Saigenji K, *et al*: Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer*　89(12)：2207-2212，2003.
4) 土屋康紀，梨本　篤，中川　悟・他：TS-1+CDDP療法1コースにてCRとなった進行胃癌の1例．癌と化学療法　33(6)：807-809，2006.
5) 亀山仁史，梨本　篤，藪崎　裕・他：TS-1/CDDP術前化学療法が奏効し原発巣が消失した進行胃癌の1例．癌と化学療法　30(10)：1485-1488，2003.
6) 山口健太郎，中川　悟，藪崎　裕・他：Paclitaxel-Low-Dose FP術前化学療法が奏効し原発巣が消失した進行胃癌の1例．癌と化学療法　33(8)：1163-1166，2006.
7) 中川　悟，梨本　篤，藪崎　裕：腹腔内細胞診陽性胃癌に対する術前化学療法の意義．癌と化学療法　33(12)：1774-1776，2006.
8) 藪崎　裕，梨本　篤，田中乙雄：高度進行胃癌に対する術前化学療法としてのTS-1/CDDP併用療法の意義．癌と化学療法　30(12)：1933-1940，2003.

Gastric Cancer (2009) 12: 10–15
DOI 10.1007/s10120-008-0465-8

Review article

Adjuvant chemotherapy with 5-FU or regimens including oral fluoropyrimidine for curable gastric cancer

Mitsuru Sasako

Department of Surgery, Hyogo College of Medicine, 1-1-Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

Abstract
Since 2000, several studies have reported positive results in reasonable-size randomized controlled trials of adjuvant treatment for potentially curable gastric cancer. At present, postoperative adjuvant chemoradiotherapy and perioperative chemotherapy are the standard of care in the United States and Europe (including Great Britain), respectively, while postoperative S-1 monotherapy is the standard of care in Japan. The effect of adjuvant treatment varies according to the type of surgery, and the best results so far have been observed in the adjuvant chemotherapy of TS-1 for gastric cancer (ACTS-GC) trial, in which D2 surgery followed by S-1 monotherapy was tested. The role of radiotherapy after D2 dissection remains unclear.

Key words Adjuvant treatment · Fluorouracil · Chemoradiotherapy · Gastric cancer

Introduction

A meta-analysis of the randomized controlled trials (RCTs) on adjuvant chemotherapy for curable gastric cancer reported the efficacy of the treatment in 2000 [1], although there had been no pivotal study showing the benefit of adjuvant treatment before 2000. In this century, however, several reports have presented the efficacy of adjuvant treatment for gastric cancer.

Results of Western trials

Intergroup study of adjuvant chemoradiotherapy [2]

Macdonald et al. [2] reported the results of the Intergroup 0116/South West Oncology Group (SWOG) 9008 study in 2001; the study was performed to evaluate the efficacy of adjuvant treatment comprising the administration of 45-Gy radiotherapy and five courses of chemotherapy consisting of 5-fluorouracil (5-FU) and leucovorin. Postoperative adjuvant chemoradiotherapy (CRT) showed a statistically significant improvement of relapse-free survival (RFS) and overall survival (OS) for patients with gastric cancer undergoing curative surgery, compared with surgery alone as control. The 3-year OS after CRT was 50%, while that of the surgery-alone group was 41% (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.09–1.66; $P = 0.005$). The chemotherapy used in this study, 5-FU and leucovorin, was a slightly-out-of-date regimen, but the low toxicity and high compliance of this treatment could have been the key to this successful study.

The study had two major weak points. First, only 10% of patients underwent D2 dissection in spite of the recommendation of D2 dissection in the protocol, suggesting that poor local control by surgery was salvaged by radiotherapy. Secondly, 35 % of the irradiation plans had major or minor deviations, most of which could be revised before actual treatment by the central quality controller. The eventual rate of major deviation was 6.5%. This happened in the United States, where the standard level of radiotherapy seems to be much higher than that in most other countries, including Japan. This fact should be taken into consideration when this treatment is adopted in other countries.

After this result came out, the standard treatment after potentially curative surgery for node-positive patients in the United States has been postoperative CRT. At present, we cannot see any United States clinical phase III trial of adjuvant treatment for potentially curable gastric cancer in the registry of the NCI (http://www.clinicaltrial.gov.)

MAGIC trial [3]

Cunningham et al. [3] reported the results of the MAGIC trial, which was performed to evaluate the efficacy of

Offprint requests to: M. Sasako
Received: March 24, 2008 / Accepted: April 24, 2008

Table 1. List of reviewed trials

Author	Accrual period	No. of patients analyzed	Chemotherapy	3-Year OS (%)		5-Year OS (%)		HR	*P* value
				ACT	Surgery	ACT	Surgery		
Nakajima T [11]	1988–1992	579	MMC+5FU, UFT			85.8	82.9	0.738	0.17
Macdonald [2]	1991–1998	556	5-FU+Leu, Rad (45 Gy)	50	41			0.74	0.005
Nashimoto [12]	1993–1994	252	MMC+5FU+AraC, UFT			91.2	86.1	NA	0.14
Neri [4]	1989–1991	137	Epirubicin+5FU+Leu			30.2	12.6	0.51	<0.01
Bajetta [6]	1992–1997	271	Etopo+Adria+CDDP			52	48	0.93	0.87
Chipponi [7]	1989–1997	199	CDDP+5FU+Leu			39.0	38.7	NA	NA
Bouche [8]	1989–1997	260	5FU+CDDP			46.6	41.9	0.74	0.063
Nitti [9]	1990–1998	191+206	FAMTX+Leu, FEMTX+Leu			43	44	0.98	0.86
De Vita [10]	1996–2001	225	Epirubicin+Leu+5FU+Etopo			48.0	43.5	0.91	0.61
Nakajima [14]	1997–2001	190	UFT			86	73	0.48	0.017
Cunningham [3]	1994–2002	503	Epirubicin+CDDP+5FU			36.3	23.0	0.75	0.009
Sakuramoto [15]	2001–2003	1059	S-1	80.1	70.1			0.68	0.003

ACT, adjuvant chemotherapy; HR, hazard ratio; MMC, mitomycin C; 5FU, 5-fluorouracil; Leu, leucovorin; Rad, radiation; AraC, cytarabine; Etopo, etoposide; Adria, adriamycin; CDDP, cisplatin; UFT, uracil-tegafur; FAMTX, 5-fluorouracil + adriamycin + methotrexate; FEMTX, 5-fluorouracil + epirubicin + methotrexate; NA, not available

perioperative chemotherapy (three cycles each before and after surgery). The chemotherapy (ECF) used for this trial was a combination of epirubicin (50 mg/m^2; day 1), cisplatin (60 mg/m^2; day 1), and 5-FU [200 mg/m^2/day; continuous intravenous administration (civ) days 1–21]. This treatment showed statistically significant improvement of both PFS and OS compared with surgery alone as control. The 5-year OS was 36.3% in the chemotherapy group and 23.0% in the surgery-alone group. There were 100 participating hospitals with no active quality control of surgery. Therefore, only about 53% of curable patients underwent D2 dissection. Secondly, 14.5% of the patients had adenocarcinoma of the esophagus, requiring a different type of surgery. Thirdly, shortly after randomization, 9 of 253 patients allocated to surgery alone did not undergo surgery or no information about surgery was available for them. If the quality of eligibility assessment had been reasonable, it would have been impossible that so many of the randomized patients did not undergo surgery. Fourthly, among 198 patients who underwent surgical resection, the pathological T stage was unknown in 5 patients and the pathological nodal stage was unknown in 42 patients. These facts strongly suggest that the quality of this trial was much poorer than those of the Intergroup 0116/SWOG 9008 study and Japanese studies. In the MAGIC trial, as the OS of curable patients in the surgery-alone group was not reported separately, comparison of results with those of other clinical trials which included only curable patients is almost impossible. However, the tumors resected in the control group were not more advanced than those included in the Intergroup 0116/SWOG 9008 study or in Japan Clinical Oncology Group (JCOG) studies.

Other clinical phase III trials with surgery alone as the control arm

In this century, six other articles reporting the results of RCTs of adjuvant chemotherapy with surgery alone as a control could be found. All but one included 5-FU as a component of the regimen. In 2001, Neri et al. [4] reported the results of a small RCT including 137 patients in total. The chemotherapy used was a combination of epirubicin, 5-FU, and leucovorin (EFL). In this paper, they reported a statistically significant survival benefit for chemotherapy over surgery alone ($P < 0.01$) [4]. However, the number reported in the interim analysis of the same trial published in 1996 [5] was different from the report of their final analysis [4], suggesting a low quality of this trial. None of the other five studies showed statistically significant differences between treatment and observation after surgery [6–10]. Table 1 shows the results of these trials. One of them was a combined analysis of two trials including 191 and 206 patients. The common aspect of these six trials is the limited number of patients enrolled in each study, fewer than 300 if combined analysis is divided by trial. None of these studies showed a statistically significant difference between the arms, which might have been reached if they had had 500 patients in one arm.

Results of Japanese clinical trials

JCOG 8801 [11]

Nakajima et al. [11] reported the results of an RCT comparing adjuvant chemotherapy using a combination of mitomycin (MMC; 1.4 mg/m^2) + 5-FU (166.7 mg/m^2),

twice weekly for 3 weeks, followed by oral administration of uracil-tegafur (UFT; 300 mg daily) for 18 months, with surgery alone as control. They enrolled 579 patients with exclusively serosa-negative gastric cancer in the study. The 5- year survival rates of the treatment and control arms were 85.8% and 82.9%, respectively. This difference was not statistically significant ($P = 0.17$; HR, 0.74; 95% CI, 0.50–1.09). In the subgroup analysis of this study, it was suggested that this kind of adjuvant chemotherapy trial should exclude patients with T1 tumors, regardless of the pathological node positivity.

JCOG 9206-1 [12]

Nashimoto et al. [12] reported the results of an RCT comparing adjuvant chemotherapy consisting of a combination of i.v. infusion of MMC (1.33 mg/m^2), 5-FU (166.7 mg/m^2), and cytarabine (13.3 mg/m^2) twice weekly for the first 3 weeks, followed by oral UFT (134 mg/m^2) for 18 months, with surgery alone as the control arm. In total, 252 patients were enrolled during 2 years. There was no significant difference between the two arms for either RFS or OS. The 5-year OS values in the test and control arms were 91.2% and 86.1%, respectively. The survival curves for both RFS and OS showed a small but clear separation between the groups. Comparison of these two curves suggests that the results of this study were negative due to a too-small sample size, which had low power to detect a difference. A clinical significance of 5% superiority for this stage of gastric cancer (the patients had serosa-negative gastric cancer) should be considered in relation to the adverse events and cost of this treatment. The JCOG did not carry any out any further confirmatory study of this regimen.

JCOG 9206-2 [13]

Miyashiro et al. [13] reported the results of an RCT comparing adjuvant chemotherapy (comprising the intraperitoneal administration of cisplatin [CDDP]) and combination i.v. chemotherapy, with CDDP (70 mg/m^2) and 5-FU (700 mg/m^2), followed by oral administration of UFT (266.7 mg/m^2 daily) for 12 months. There was no difference in OS or RFS (only 1% difference in 5-year OS). At the time when this study was planned, CDDP intraperitoneal and 5-FU + CDDP i.v. therapies were some of the most attractive ones that were thought to have the potential to improve OS and RFS. However, mainly due to the high toxicity of the intraperitoneal administration of CDDP, low compliance was a large problem in this study.

National Surgical Adjuvant Study of Gastric Cancer (N-SAS-GC) [14]

In the 1980s and 1990s, many Japanese surgeons used UFT in clinical practice without sufficient evidence that it improved OS and RFS after curative surgery. The Japanese government initiated an RCT to re-evaluate the efficacy of this drug and ordered the pharmaceutical company that produced UFT to take over this trial as a sponsored one to compare UFT (360 mg/m^2, 5 days on and 2 days off) versus surgery alone for pT2, pN1/2 patients. The target population of this study was selected based on the subgroup analysis of the JCOG 8801 study. Due to very slow accrual, the sponsor and the investigators decided to stop accrual after only 190 patients had been randomized. As the original projected sample size was 500, less than half of the expected number was registered. Without any expectation, these enrolled patients were followed up, but the second interim analysis showed statistically significant differences of OS and RFS between the arms in this study. Later, with full follow up, the final survival results were reported. Five-year OS values after adjuvant treatment and surgery alone were 86% and 73%, respectively ($P = 0.017$). The HR for OS in the chemotherapy group was 0.48 (95% CI, 0.26–0.89). However, there are several criticisms of this study. The number of enrolled patients was less than half of the expected sample size. The survival rate of the control arm (surgery alone) was much lower than that in the JCOG 9201-1 study, which had been carried out in almost the same period. The 5-year RFS of the surgery-alone arm in the N-SAS-GC trial was 68%, while the pT2pN1-4 subpopulation in the JCOG 9206-1 study showed a 5-year RFS of 80%.

Adjuvant Chemotherapy of TS-1 for Gastric Cancer (ACTS-GC) [15]

The ACTS-GC trial was also a sponsor-led RCT, carried out to evaluate the efficacy of S-1 monotherapy as adjuvant chemotherapy after curative D2 surgery. Pathological stage II, IIIA, and IIIB patients were randomized within 6 weeks after surgery either to S-1 administration or surgery alone. The treatment regimen comprised 6-week cycles, in which S-1 at 80 mg/m^2 per day was given for 4 weeks, with no chemotherapy for the following 2 weeks. This trial showed good patient accrual of 1059 patients within 38 months. At the first planned interim analysis, the difference between the two arms was so large that the independent data and safety monitoring committee recommended to the investigators to stop the trial and open the results. The final analysis, carried out using the updated data of 6 months later, was reported in the *New England Journal of Medicine*. The most frequent grade 3/4 toxicity was anorexia (6%),

followed by nausea (3.7%) and diarrhea (3.1%). Compliance at 6 months and at 1 year was 78% and 66%, respectively. The primary endpoint, OS at 3 years, was 80.1% in the S-1 group and 70.1% in the surgery-alone group, with an HR of 0.68 (95% CI, 0.52–0.87). The HR of the RFS was even smaller, 0.62 (95% CI, 0.50–0.77; $P < 0.001$). It was also reported that S-1 significantly reduced lymph nodal ($P = 0.01$) and peritoneal ($P = 0.009$) recurrence. Subgroup analysis showed a consistent HR of less than 1.0 in any subgroup, suggesting the applicability of the results to all subpopulations included in this study. This has been the first positive large high-quality Japanese phase III study of adjuvant chemotherapy for curable gastric cancer to have had a strong impact on clinical practice.

Comparison of Western and Japanese trials

There have been longstanding arguments regarding the large differences in OS or RFS between Western and Japanese studies. It was often mentioned that Western and Japanese studies were treating different diseases. This is true in some aspects, but not in the majority of aspects. To date, there has been no high-quality study that has reported biological differences in gastric cancer between Western and Japanese patients. Moreover, some studies report the similarity of gastric cancers in Western and Japanese patients [16, 17]. Stage migration, due to more accurate nodal staging in Japan, can explain some part of the large differences in OS and RFS[18]. To carry out fair comparison and avoid stage migration, comparison by T stage seems the most reliable method.

The two populations in the Intergroup 0116/SWOG 9008 study [2] and the JCOG 9206-2 trial [13] were by chance very similar in most aspects, suggesting that almost the same patient populations were treated in these two different studies. Table 2 shows the baseline characteristics of the randomized patients in these two trials. Unlike the actual features of gastric cancer patients in the United States, the majority of patients in the Intergroup 0116/SWOG 9008 study [2] had classic-type antral cancer of intestinal histology. There were more patients with nodal metastasis in the United States study but there were more with diffuse cancer and more with linitis plastica in the Japanese study, resulting in a good balance in terms of prognosis. The OS in the test arm of the Intergroup 0116/SWOG 9008 study [2] was 40%, while that for the entire patient cohort, including the surgery-alone group, was 61%. This large difference can be explained only by a difference in treatment, i.e., D2 dissection or D1 + radiotherapy.

Quality of surgery

Subgroup analysis of the Intergroup 0116/SWOG 9008 study suggested that no benefit of the treatment was

Table 2. Comparison of Intergroup 0116/SWOG 9008, JCOG 9206-2, and MAGIC trials

	Intergroup 0116 SWOG 9008 [2]	JCOG 9206-2 [13]	MAGIC [3]
No. of patients	281 (CRT arm)	268	253 (Surgery alone)
Tumor location			
Antrum	53%	31%	NA
Body	24%	32%	NA
Cardia	21%	28%	12%+ Eso14%
Multiple	2%		NA
All sites		9%	NA
Histological type			
Diffuse	92	162	NA
Intestinal	135	93	NA
pT stage			
T1	14	5	16
T2	75	87	55
T3	174	165	106
T4	18	18	16
T3+4	68%	65%	63%
Node-positive	85%	72%	73%
Tumor size; cm (median)		6.0	5.0
Surgery			
D0	54%	0%	0%
D1	36%	1%	28%*
D2	19%	99%	53%*
Adjuvant	5FU+Leu+Rad	5FU+CDDP+UFT	None-surgery alone
5-Year Survival	42%	61%	23% (32%**)

Eso, esophageal cancer
* % among those undergoing curative resection; ** 5-year survival rate among curable patients

observed in those who underwent D2 dissection [19]. Hundahl et al. [20] made an ad-hoc analysis of the prognostic impact of hypothetical residual nodal disease, calculated using a computer program based on a large database accumulated at the National Cancer Center Hospital in Tokyo, and found that the limited dissection which had high probability of residual disease undermined the prognosis. In other words, this study clearly demonstrated that the effect of chemoradiotherapy depended on the type of surgery.

In the ACTS-GC study [15], all patients underwent D2 dissection, while only 10% and 40% of the enrolled patients underwent D2 dissection in the Intergroup 0116/SWOG 9008 study [2] and the MAGIC trial [3], respectively. It is also possible to make a comparison between the types of surgery in the MAGIC trial and the ACTS-GC study [15] or the JCOG 9206-1 study [12]. Looking at the baseline characteristics of the patients and tumors, it is hardly acceptable that the MAGIC trial has shown good results. For Japanese standards, the results of the control arm of the MAGIC trial were extremely poor, and this could have been the reason for the positive results of this study.

Is radiation needed?

The Intergroup 0116/SWOG 9008 study [2] showed a clear benefit of CRT in those who underwent less than D2 dissection. However, there remain two clinical questions. The first question is whether D1 + CRT can replace D2 + chemotherapy alone. The second one is whether CRT can improve the results of D2 dissection. The second issue is more relevant for Japanese physicians and patients, because D2 + chemotherapy is the standard of care in Japan. There is only one study, by Kim et al. [21], reporting the results of a retrospective comparison of OS between patients who underwent D2 + postoperative CRT and those with D2 surgery alone. These authors selected 446 patients as the surgery-alone group out of 3447 patients who underwent potentially curative resection. These patients fulfilled the eligibility criteria for CRT in their institution. One of the reasons for exclusion was palliative resection, which is not consistent with the description of "curative resection" for the entire group. The results of such kinds of retrospective analysis are usually far less reliable than the results of a prospective study. There were several important differences between the two groups, D2 + CRT and D2 alone, including the age of the patients, which is known to be one of the most important prognostic factors in gastric cancer patients. We should keep in mind also that this comparison was not between D2 + CRT versus D2 + chemotherapy. The OS obtained for D2 + CRT did not seem to be superior to the OS observed in the patients who underwent D2 + chemotherapy in the ACTS-GC study [15]. In other words, the OS of those who underwent surgery alone in the study by Kim et al. [21] was far poorer than the stage-specific OS reported in the ACTS-GC study [15]. Kim and colleagues are now carrying out a single-institutional prospective RCT comparing D2 + CRT versus D2. We should wait for the results of this study. If this study shows remarkable results, Japanese physicians would have to consider the benefit of the addition of radiotherapy over D2 + chemotherapy.

Future directions

Through this review, it appears that the achievement of the ACTS-GC study [15] should be highly appreciated, and for the moment the standard of care for stage II/III gastric cancer is D2 surgery followed by postoperative adjuvant chemotherapy with S-1 for 1 year. As the results of surgery alone in Japan are acceptably good for stage II patients, the next question might be whether we can reduce the total dose and period of adjuvant treatment with S-1 for these patients. An RCT of noninferiority design to compare 6 months' and 12 months' administration of S-1 might be an interesting trial, because the standard length of adjuvant chemotherapy for other cancers in Western countries is usually 6 months. For more advanced stages, more effective chemotherapy is expected. Careful selection of the next candidate treatment for the test arm of an adjuvant phase III trial for curable stage III gastric cancer is now ongoing; this is being done by carrying out feasibility studies using some regimens that show better OS than S-1 alone for advanced or metastatic gastric cancer. If such regimens cannot be given postoperatively, preoperative administration might be another way to go.

References

1. Oba K, Morita S, Tsuburaya A, Kodera Y, Kobayashi M, Sakamoto J. Efficacy of adjuvant chemotherapy using oral fluorinated pyrimidines for curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials in Japan. J Chemother 2006;18:311–7.
2. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.
3. Cunningham D, Allum WH, Stenning SP, Thompson JN, van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
4. Neri B, Andreoli F, Boffi B, Francesconi D, Mazzanti R, Medi F, et al. Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow up. Br J Cancer 2001;84:878–80.

5. Neri B, de Leonardis V, Romano S, Andreoli F, Pernice LM, Bruno L, et al. Adjuvant chemotherapy after gastric resection in node-positive cancer patients: a multicentre randomised study. Br J Cancer 1996;73:549–52.
6. Bajetta E, Buzzoni R, Mariani L, Beretta E, Bozzetti F, Bordogna G, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomized study by the Italian Trials in Medical Oncology (ITMO) Group. Ann Oncol 2002;13:299–307.
7. Chipponi J, Hugier M, Pezet D, Basso N, Hay JM, Quandalle P, et al. Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. Am J Surg 2004;187:440–5.
8. Bouché O, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton M, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer; 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol 2005; 16:1488–97.
9. Nitti D, Wils J, Dos Santos JG, Fountzilas G, Conte PF, Sava C, et al. Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI Group and the ICCG. Ann Oncol 2006;17:262–9.
10. De Vita F, Giuliani F, Orditura M, Galizia G, Di Martino N, Montemurro F, et al. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase IIItrial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). Ann Oncol 2007;18:1354–8.
11. Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomized trial. Lancet 1999;354:273–7.
12. Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, et al. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer; Japan Clinical Oncology Group 9206–1. J Clin Oncol 2003;21:2282-7.
13. Miyashiro I, Furukawa H, Sasako M, Yamamoto S, Nashimoto A, Nakajima T, et al. No survival benefit with adjuvant chemotherapy for serosa-positive gastric cancer: randomized trial of adjuvant chemotherapy with cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer. Presented at the 2005 Gastrointestinal Cancers Symposium; 2005 January 27–29; Hollywood, FL, USA. Alexandria, VA, American Society of Clinical Oncology; 2005.
14. Nakajima T, Kinoshita T, Nashimoto A, Sairenji M, Yamaguchi T, Sakamoto J, et al. Randomized controlled study of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg 2007;94:1468–76.
15. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357: 1810–20.
16. McCulloch PG, Ochiai A, O'Dowd GM, Nash JR, Sasako M, Hirohashi S. Comparison of the molecular genetics of c-erb-B2 and p53 expression in stomach cancer in Britain and Japan. Cancer 1995;75:920–5.
17. Bonenkamp JJ, van de Velde CJ, Kampschöer GH, Hermans J, Hermanek P, Bemelmans M, et al. Comparison of factors influencing the prognosis of Japanese, German, and Dutch gastric cancer patients. World J Surg 1993;17:410–5.
18. Bunt AMG, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathological stage migration confounds comparisons of gastric cancer survival rates between Japan and western countries. J Clin Oncol 1995;13:19–25.
19. Macdonald JS, Smalley S, Benedetti J, Estes N, Haller D, Ajani JA, et al. Presented at the 2004 Gastrointestinal Cancers Symposium; 2004 Jan 22–24; San Francisco, CA, USA. Alexandria, VA, American Society of Clinical Oncology; 2004.
20. Hundahl SA, Macdonald JS, Benedetti JB, Fitzsimmons T. Surgical treatment variation in a prospective randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol 2002;9:278–86.
21. Kim SK, Lim DH, Lee JY, Kang WK, Macdonald JS, Park CH, et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiotherapy in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005;63:1279–85.

Gastric Cancer (2009) 12: 37–42
DOI 10.1007/s10120-008-0496-1

Original article

Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002)

Taira Kinoshita[1], Mitsuru Sasako[2], Takeshi Sano[3], Hitoshi Katai[4], Hiroshi Furukawa[5], Akira Tsuburaya[6], Isao Miyashiro[7], Masahide Kaji[8], and Motoki Ninomiya[9] (on behalf of the Gastric Cancer Surgery Study Group of the Japan Clinical Oncology Group)

[1] Department of Surgical Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
[2] Department of Surgery, Hyogo College of Medicine, Kobe, Japan
[3] Department of Surgery, Cancer Institute Hospital, Tokyo, Japan
[4] Department of Surgical Oncology, National Cancer Center Hospital, Tokyo, Japan
[5] Department of Surgery, Sakai Municipal Hospital, Osaka, Japan
[6] Department of Surgical Oncology, Kanagawa Prefectural Cancer Center Hospital, Yokohama, Japan
[7] Department of Surgery, Osaka Medical Centre for Cancer and Cardiovascular Diseases, Osaka, Japan
[8] Department of Surgery, Toyama Prefectural Central Hospital, Toyama, Japan
[9] Department of Surgery, Hiroshima City Hospital, Hiroshima, Japan

Abstract

Background. **The prognosis of scirrhous gastric cancer remains poor despite extended surgery or adjuvant or neoadjuvant chemotherapy. A pilot study of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral 5-fluorouracil derivative, for neoadjuvant chemotherapy unexpectedly showed good response and a promising effect on survival. Therefore, the Japan Clinical Oncology Group conducted a phase II trial to confirm the efficacy of S-1 for neoadjuvant chemotherapy against resectable scirrhous gastric cancer.**

Methods. **Patients were eligible if they had typical scirrhous gastric cancer invading more than half of the stomach, and resectable disease confirmed by laparoscopic staging. The treatment schedule consisted of two courses (each, 4-week administration and 2-week withdrawal) of S-1 (100–120 mg/body per day), followed by radical surgery.**

Results. **Fifty-five eligible patients were registered. Three completed only one course of the neoadjuvant chemotherapy, whereas 52 completed two courses. Toxicity was acceptable, with a few grade 3 (5.5%) events, but no grade 4 adverse events. The response rate was 32.6% in 43 evaluable patients. Of the 55 patients, 2 refused operation, 1 developed lung metastasis, and 52 underwent laparotomy. The curative resection rate was 80.8%, with acceptable morbidity and no mortality. The survival curve at 2 years' follow up showed a better survival rate than that of the historical controls, but did not reach the expected survival rate.**

Conclusion. **S-1 neoadjuvant chemotherapy appeared feasible and showed positive effects against scirrhous gastric cancer; however, the survival rate with S-1 did not reach the expected rate required when selecting an agent for a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy against scirrhous gastric cancer.**

Offprint requests to: T. Kinoshita
Received: September 16, 2008 / Accepted: November 27, 2008

Key words Scirrhous gastric cancer · Neoadjuvant chemotherapy · S-1

Introduction

Scirrhous gastric cancer, also known as linitis plastica or Borrmann type 4, is a special type of stomach cancer known for its very poor prognosis. It is very difficult to identify this cancer in its early stage, and even aggressive surgical procedures and adjuvant chemotherapies have not considerably improved the survival rate in patients with this neoplasia. Owing to its low incidence, only a few drug trials against this neoplasia have been conducted thus far. On the other hand, several studies of neoadjuvant chemotherapy against scirrhous gastric cancer have suggested the efficacy of such treatment [1–4]. However, all these studies involved a small sample size and they usually did not determine the survival benefits of such treatment. Furthermore, a phase II trial of sequential high-dose methotrexate and fluorouracil combined with doxorubicin (FAMTX) for neoadjuvant chemotherapy has shown moderate toxicity and no survival benefits [5]. Interestingly, S-1, which is a dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine, has shown the highest response rate among many oral anticancer agents against unresectable advanced gastric cancer in early and late phase II trials [6–8]. In these late phase II trials, S-1 showed a 33% response rate against scirrhous gastric cancer. Because of the reported promising effects of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer in a previous pilot study [9], the Japan Clinical Oncology Group

(JCOG) decided to conduct a phase II trial to determine survival benefits of S-1 treatment.

Patients, materials and methods

Patient eligibility

Patient eligibility required the fulfillment of the following criteria: histologically confirmed gastric adenocarcinoma; potentially resectable laparoscopy-confirmed typical scirrhous gastric cancer (without definitive ulceration) that invaded more than half of the stomach; received no prior treatment; 70 years or younger; Eastern Cooperative Oncology Group performance status of 0 or 1; and oral intake possible. Patients also had to have adequate organ functions (creatinine clearance, ≥50 ml/min; blood urea creatinine, within the institutional limit; GOT and GPT, within twice the institutional limit; leukocytes, 3500/mm^3≤ leukocyte <12 000/mm^3; hemoglobin, ≥9.0 g/dl; thrombocytes, ≥100 0000/mm^3; total bilirubin, within twice the institutional limit; and normal electrocardiogram).

Diagnostic and staging procedures included physical examination, barium gastrography, endoscopy, chest X-ray, abdominal computed tomography (CT) scan, and laparoscopy with cytological examination of peritoneal washing of the Douglas pouch. Patients with positive cytology on peritoneal washing and potentially resectable disease without visible peritoneal dissemination were also included in the study.

This study was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

Treatment schedule

Chemotherapy consisted of two courses (4-week administration and 2-week withdrawal) of S-1 at 100–120 mg/body per day. After two courses of neoadjuvant chemotherapy, patients were reevaluated for the presence of potentially resectable disease and those who were positive underwent laparotomy. Because two patients underwent endoscopic examination after one course of chemotherapy and stopped chemotherapy due to progressive disease, the treatment protocol was revised such that the evaluation of the effect of neoadjuvant chemotherapy should be carried out only after two courses and only by fluoroscopic examination. If indicated, patients received curative or palliative resection or exploratory laparotomy within 14 days after completing the second course of adjuvant chemotherapy. Patients with curative resection were followed up without any adjuvant chemotherapy every 3 months until cancer relapse.

Evaluation of response and toxicity

Potentially resectable scirrhous gastric cancer usually shows no measurable lesions, except for primary foci. We decided to evaluate the response of only primary foci following chemotherapy. Because it is very difficult to evaluate the response of the primary foci using the Response Evaluation Criteria in Solid Tumors criteria, we used a National Institutes of Health (NIH) image to calculate the barium-filling area or whole stomach on a double-contrast fluoroscopic examination study, as well as to compare the area before and after chemotherapy. Responses were classified as partial response (PR), more than 50% increase in the area after chemotherapy; stable disease (SD), 0 to less than 50% increase in the area; and progressive disease (PD), any decrease in the area and the appearance of new lesions. National Cancer Institute Common Toxicity Criteria ver2.0 were employed for determining chemotherapy toxicity.

Pathological assessment was performed to evaluate disease extent, resection margins, and response to chemotherapy as evidenced by the presence of necrotic and cancer cells. The pathological response to chemotherapy was classified according to the following criteria provided by the Japanese Gastric Cancer Association [10]: grade 0, absence of necrosis or degeneration; grade 1a, necrosis or degeneration is observed in less than one-third of the tumor; grade 1b, less than two-thirds and more than one-third of the tumor show necrosis or degeneration; grade 2, more than two-thirds of the tumor shows necrosis or degeneration; grade 3, all tumors show necrosis or degeneration.

Historical controls

Because we applied laparoscopic staging to exclude patients with visible peritoneal dissemination, it was very difficult to find good historical controls. Laparoscopic staging had gained popularity at the commencement of this trial; however, we had no identical historical controls. The historical controls consisted of 241 patients who had the same lesions as those described in the eligibility criteria for this study, and who had no visible peritoneal dissemination at laparotomy without laparoscopic staging, and had been treated at the participating institution during 1991–1993. Data for the historical controls were as follows: 2-year survival rate, 45%; curative resection rate, 90.3%; 30-day operative mortality rate, 1.2%; and in-hospital mortality rate, 3.5%.

Statistical considerations

The primary endpoint of this study was the 2-year survival rate. Fifty-five patients were required to be registered on the basis of the expectation that the 2-year survival rate of those receiving this neoadjuvant chemo-

therapy would be 60% (15% higher than that of the historical controls), allowing 10% of ineligible patients. Survival time was calculated from the initial date of the initiation of neoadjuvant chemotherapy to the date of death or the last follow-up date. Survival data were analyzed according to the method of Kaplan and Meier and then compared with the data of the historical controls.

Results

Patient accrual

From March 14, 2001, to February 4, 2003, 55 patients were enrolled in the study from 15 institutions. The mean age was 56 years (range, 31–70 years).

Neoadjuvant chemotherapy

The patients were composed of 26 male and 29 female patients. The scheduled two courses of neoadjuvant chemotherapy were performed in 52 patients. The remaining 3 patients received one course, because 2 of the 3 patients were judged to have PD by endoscopic evaluation after one course before the revision of the protocol, and 1 patient was found to have advanced bile duct carcinoma after one course of chemotherapy. These 3 patients received curative resection after one course of neoadjuvant chemotherapy. There was no chemotherapy-induced grade 4 adverse reaction in the cohort. Only 3 patients developed grade 3 adverse reactions (Table 1).

As mentioned earlier, the effect of adjuvant chemotherapy was evaluated from the change in the barium-filling area before and after the chemotherapy, as calculated from the NIH images. Among the 43 patients whose fluoroscopic films could be evaluated, 14 patients (32.6%) showed more than 1.5 times enlargement of the stomach (PR); 13 patients showed SD (30.2%), and 16 patients showed PD (37.2%).

Table 1. Adverse reactions

	Grade				%	
	0	1–2	3	4	Grade 4	Total
T. Bil	32	23	0	0	0	55
WBC	42	13	0	0	0	55
Neutrophils	42	12	1	0	0	55
ALT	43	11	2	0	0	55
AST	45	9	0	0	0	55
Hb	48	7	0	0	0	55
Nausea/vomiting	36	19	0	0	0	55
Pigmentation	44	11	0	0	0	55
Anorexia	45	10	0	0	0	55
Diarrhea	45	10	0	0	0	55
Stomatitis	45	10	0	0	0	55
General fatigue	46	9	0	0	0	55

Only three patients developed grade 3 adverse reactions, and they recovered by withdrawal of S-1
T. Bil, serum total bilirubin; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin

Operation

Among the 55 patients, 3 did not undergo operation, because of the refusal of 2 and because the other patient was found to have pulmonary metastases. Fifty-two patients underwent laparotomy, including the 3 patients who received one course of the neoadjuvant chemotherapy. Among the 52 patients, 6 patients did not undergo resection (5, peritoneal dissemination; 1, unresectable invasion of the duodenum and pancreatic head). Ten patients underwent palliative resection of the main tumor (2, peritoneal dissemination; 6, positive cytological examination of abdominal washing; 1, unresectable tumor with severe invasion to the retroperitoneum; 1, widespread lymph node metastases). The other 36 patients underwent curative total gastrectomy with various combined organ resections (25, spleen; 1, distal pancreas + spleen; 5, gallbladder; 2, left adrenal gland; 2, transverse colon; 1, pancreatic head and duodenum). Among the 36 patients, only 1 had D1 lymph node dissection and the remaining 35 had D2 or more lymph node dissection.

The mean operation time for curative resection was 214 min (range, 130–460 min) and that for noncurative resection was 295 min (range, 150–401 min). The mean blood loss for curative resection was 586 ml (range, 30–1815 ml) and that for noncurative resection was 872 ml (range, 230–2100 ml).

Among the 46 patients who underwent resection, postoperative complications were observed in 11 patients (23.9%). Overall, there was no mortality and there were no serious complications. The actual complications were as follows: wound infection, deep vein thrombosis, pancreatic fistula, anastomotic ulcer, pneumonia, pulmonary embolism, sepsis, abdominal abscess, liver function disorder, and mycotic uveitis.

Changes in the T, P, and CY (cytological examination of the abdominal washing) factors before and after neoadjuvant chemotherapy are shown in Tables 2 and 3. With regard to the T factor, a response was observed in 14 patients; however, cancer progression was observed in 8 patients. In regard to the P and CY factors, a response (PR) was observed in only 2 patients; however, 10 showed progressive disease (PD). The other 40 patients showed stable disease (SD).

The pathological therapeutic effects of neoadjuvant chemotherapy were evaluated according the grading described by the Japanese classification of gastric carci-

noma [10] general rules for gastric cancer study: grade 0, 12 patients (26.1%); grade 1a, 19 patients (41.3%); grade 1b, 4 patients (8.7%), and grade 2, 11 patients (23.9%).

At the time of the scheduled analyses (March 2005), 10 patients were still alive without recurrence, 13 were alive with recurrence, and 32 had already passed away. The modes of recurrence were as follows: peritoneal, 17 patients; retroperitoneal, 2 patients; local, 1 patient; lymph node, 1 patient.

Table 2. Changes in T factors before and after chemotherapy

Laparoscopic T		Pathological T
T2:7		T2:11
T3:39	Chemotherapy	T3:37
T4:5		T4:4
Tx:1		

Progression, 8 patients; downstage, 14 patients
Tx, T unknown

Table 3. Changes in P and CY factors before and after chemotherapy

No change or progression (SD and PD)	
P0, CY0→P0,CY0	37 (SD)
P0, CY0→P0, CY1	2 (PD)
P0, CY1→P0, CY1	3 (SD)
P0, CY0→P1	4 (PD)
P0, CY1→P1	4 (PD)
Downstage (PR)	
P0, CY1→P0, CY0	2 (PR)

The survival curves of all patients (n = 55) and the historical controls are shown in Fig. 1. The survival curve of the study arm was better than that of the historical controls; however, the survival rate did not reach the expected rate (2-year survival rate: 59% vs 60%).

With regard to the secondary endpoints, the response rate to the neoadjuvant chemotherapy was 32.6%. The rate of postoperative complications was 23.9%, as against 25.7% in the historical controls. The in-hospital mortality rate was 0% as against 3.5% in the historical controls. The curative resection rate was 80.8%, as against 90.3% in the historical controls.

Discussion

Despite recent advances in chemotherapy and extended surgery, the treatment outcomes of scirrhous gastric cancer, also known as diffuse gastric cancer, linitis plastica, or Borrmann type 4 in the West, have remained very poor because of the aggressive biological behavior of this tumor. Because of failure to improve survival even with aggressive postoperative chemotherapy, neoadjuvant chemotherapy has been applied to patients with resectable or unresectable scirrhous gastric cancer.

To date, the efficacy of neoadjuvant chemotherapy against scirrhous gastric cancer remains to be established because of the lack of well-validated phase II and phase III studies. The first phase II neoadjuvant chemotherapy trial was reported by Takahashi et al., using FAMTX [5]. In their trial, neoadjuvant chemotherapy was shown to be seemingly feasible against scirrhous

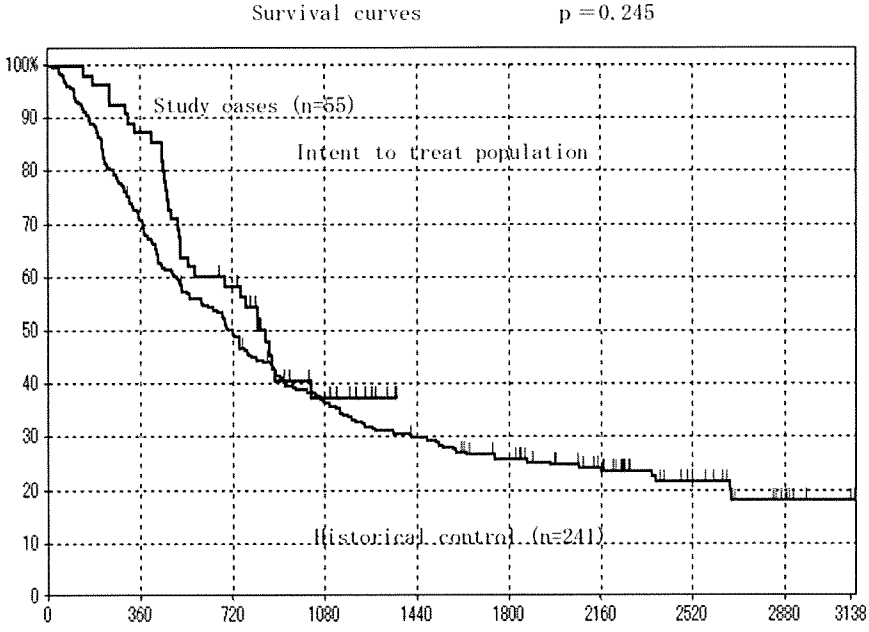


Fig. 1. Survival curves of all patients (n = 55) and the historical controls (n = 241)