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Adjuvant Therapy for Advanced Gastric Cancer

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Although many randomized control trials (RCT) as to adjuvant therapy for advanced gastric cancer have been run since 1950s, an efficacy of this therapy has not been proven yet. Because most of doctors had little understanding of RCT or biological statistics, good study had not been carried out especially in Japan. Recently well designed RCTs have been run and some of them have reported positive result. Meta-analyses also have suggested positive effect of adjuvant chemotherapy. However, the introduction of positive data in foreign studies to our country faces many problems because of differences in operative procedure, such as an extent of lymphadenectomy, body type of patients, and so on. Japanese surgeons and medical oncologists have to continue our efforts to establish evidence which is applicable for Japanese gastric cancer patients.

● 特 集 ● 腹膜転移の治療

腹膜転移を有する初発胃癌の治療戦略

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〔*Jpn J Cancer Chemother* 32(10): 1398-1403, *October*, 2005〕

Treatment Strategy for Primary Gastric Cancer with Peritoneal Dissemination: Takaki Yoshikawa, Akira Tsuburaya and Osamu Kobayashi (*Dept. of Gastrointestinal Surgery, Kanagawa Cancer Center*)

Summary

Curative resection is considered to be a standard therapy for gastric cancer with localized peritoneal metastases. For tumors with diffuse dissemination, chemotherapy may play a major role, however, the benefits of reduction surgery and standard chemotherapy have not yet been clarified. Median survival time after reduction surgery was reported to be 4-13 months for patients diagnosed by surgery and/or CT and 5-6 months for chemotherapy for those diagnosed by CT alone. Reduction surgery has a high risk, with a morbidity of 12-44% and a mortality of 3-14%. Palliative surgery should be indicated for stenosis or bleeding due to primary tumors. 5-FU, MTX-5-FU, TS-1, paclitaxel, and their combination are candidates for practice and clinical trials. It is important to evaluate the severity of peritoneal dissemination by diagnostic laparoscopy or laparotomy for decision making. **Key words**: Gastric cancer, Peritoneal metastasis, Treatment strategy, **Corresponding author**: Dr. Takaki Yoshikawa, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan

要旨　限局した腹膜転移症例では，根治切除術が標準的治療と考えられている。一方，根治切除できない腹膜転移に対しては化学療法が主体となるが，減量手術を先行すべきか，化学療法の標準 regimen は何か，いまだ解明されていない。減量手術の MST は 4〜13 か月，化学療法では 5〜6 か月と報告されているが，対象が異なっている。自験例 P2P3 症例の MST は CT 所見あり 5 か月，なし 7.7 か月と，化学療法の対象となるような CT 所見を有する場合の予後は短い。一方，減量手術の morbidity と mortality は高く，それぞれ 12〜44%，3〜14%と報告されている。原発巣に伴う出血や狭窄がある場合には，緩和手術の適応となる。化学療法の regimen としては 5-FU, MTX/5-FU, 低分化型腺癌に有効で腹腔内移行も良好な TS-1 や paclitaxel，これらの combination などが候補と考えられるが，今後適切な臨床試験が必要である。治療方針決定のためには，腹腔鏡または試験開腹により腹膜転移の重症度を評価することが重要である。

緒　言

胃癌が治癒するためには，肉眼的に遺残なく癌を取りきること（根治切除）が必要不可欠である[1]。一方，根治切除できない腹膜転移を伴う胃癌に対しては，化学療法が主体となる場合が多いが，化学療法の標準 regimen は何か，減量手術を先行するべきか否か，いまだ解明されていない。本論文では，現時点で得られる evidence を基に，腹膜転移を有する初発胃癌に対する治療戦略について考察した。

I. 手　術

1. 根治切除術

本邦では，過去の膨大な手術病理所見の詳細な解析と解剖学的見地から，2 群リンパ節郭清と大網盲嚢切除を伴う D2 定型手術が確立された[2]。胃癌がこの局所治療範囲内に肉眼的にとどまっている場合，D2 手術は根治切除の標準とされている。腹膜転移においても例外ではなく，転移が横行結腸より頭側にのみ存在し，通常の D2＋大網盲嚢切除で取り切れる範囲に存在する場合，局所治療である D2 定型根治切除が行われてきた[3]。その結果治癒する症例が少なからず存在することが明らかと

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0385-0684/05/¥500/論文/JCLS

表1 減量手術のmedian survival time (MST) と合併症，手術死亡

転移部位	MST (M)	合併症 (%)	手術死亡 (%)	在院死 (%)	文献
P2, P3	8.6	24.1	3.4	13.8	5
P2, P3	12.2	—	2.5*	—	7
P2, P3	7	—	—	1.6**	8
Any	8.1	38	12	—	9
Any	8.4	37	10	—	10
Any	5.5〜10.0	—	13	—	11
Any	8.0	—	11.5	—	12
Any	9.5***	42	7	—	13
Any	4〜6	44	11	—	14
Any	9	37.5	11.3	—	15
Any	10.6	49.0	7.0	—	16
Any	12.7	11.7	2.8	—	17

*: バイパス術，試験開腹術を含む
**: P以外の原因による減量切除術を含む
***: mean survival time

なっている[3]。現時点では化学療法のみで治癒することがほとんどないのに対して，これらの群の5年生存率が10%程度存在する[3]，median survival time (MST) が1〜2年程度[4]と明らかに良好であることから，このような症例に対して根治切除を行うことは標準的治療と考えられる。

D2定型手術の範囲を超えて，腹膜転移が広汎に広がっている場合には，通常，根治切除の適応とはならない。当院におけるMSTは旧P2症例で8.8か月，旧P3症例で5.6か月と予後不良である[5]。D2定型切除範囲外に数個しか腹膜播種結節が存在せず，過大侵襲なく完全切除が可能な場合に根治切除すべきかどうかについてのevidenceはない。しかしながら，まれに治癒することがあるため，根治切除が選択されることもある。JCOG胃癌外科グループでのアンケートによると，腹膜転移巣が肉眼的に取りきれる場合には根治切除を重視すると考える施設が多かった[6]。

2．原発巣の減量手術

広汎な腹膜転移を有する症例で，通常のD2で根治切除が不可能と判断される場合に原発巣を切除すべきかどうかについてのevidenceはない。腹膜転移や肝転移を含めた非治癒因子を有する初発胃癌症例のretrospective studyでは，非切除群に対して減量手術群で，予後の延長がみられたとする報告が多い[7-15]。特に非治癒因子が一つに限定される場合に減量手術が有効であるとする報告が多い。減量手術によるMSTは，減量手術後の多様な抗癌剤治療を含めて4〜13か月と報告されている（表1）。腹膜転移単独の非治癒因子群を対象とした解析では，減量手術が有効とする報告[7]，有効でないとする報告[5,10]がある。しかしながら，これらの報告はすべてretrospectiveに解析しているため，減量手術群と非切除群との間に明らかな背景因子の偏りがある。われわれの検討では，背景因子を可能なかぎり分析して組み入れた多変量解析を行った場合，非緩和目的の減量切除は予後因子とはならなかった[5]。

減量手術は化学療法の効果を前提にするものであり，そのcomplianceは生存期間に重大な影響を及ぼす。合併症を起こした場合，化学療法を開始することができず，在院死に直結する。これまでの報告では，減量手術のmorbidityは12〜44%，mortalityは3〜14%と報告されている（表1）。D2 vs D4 phase III試験（JCOG 9501）におけるD2群のmorbidityは20.9%，mortalityは0.8%であった[18]ことを考慮すると，減量手術の危険性ははるかに高いために十分なICが必要である。

3．緩和手術

原発巣による出血や狭窄症状が存在する場合，化学療法が困難なことが多いため，根治切除可能か否かにかかわらず積極的な緩和手術の適応となる[5]。しかしながら，緩和目的の減量手術の場合でもmorbidityとmortalityが高いことを十分に考慮し，バイパス手術，stentやIVRなどの手段で緩和可能か否か，best supportive careとすべき症例かどうか，適切に判断する必要がある。われわれの過去の症例の解析では，初発P2/P3症例における切除は，緩和目的の手術に限られる，という結果であった[5]。

II．化学療法

これまでに，腹膜転移症例のみを対象として化学療法を行った前向き臨床試験の報告はない。切除不能進行再発胃癌に対する化学療法のphase IIIでは，MSTは7〜9か月である[19-22]。一方，前向き臨床試験の腹膜転移症例に限ったsubset解析では，tegafur＋MMC vs UFT＋

MMC の randomized phase II試験において5か月[23]，MTX+5-FU 時間差療法（MF）の phase II試験において6か月であった[24]。化学療法の臨床試験では，適格基準に CT もしくは消化管造影検査で明らかに腹膜転移と診断できることが含まれている。当院で開腹術または腹腔鏡検査を行い P2P3 と診断した群における MST は，CT 所見あり5か月，CT 所見なし7.7か月と，CT 所見を有する症例の予後は有意に不良であった[25]。このように，化学療法の対象（CT で腹膜転移所見を有する症例）と減量切除の対象（CT 所見はなく開腹または腹腔鏡検査で腹膜転移と診断した症例）では腹膜転移の重症度が異なっており，単純に MST を比較することはできない。

腹膜転移では，腸管狭窄によるイレウス，尿管狭窄による水腎症，腹水貯留などにより，容易に PS が低下する。CT で明らかに腹膜転移と診断できる病態では，臨床試験の適格基準を満たす症例においても5〜6か月[23,24]と，切除不能進行再発胃癌症例を対象とした best supportive care（BSC）症例の3〜4か月[26-28]よりわずかに良好といえる程度である。これらの BSC は TPN などの積極的な緩和医療を行っているわけではなく，画像上明らかな腹膜転移に対する化学療法の意義は適切な臨床試験で検証する必要があろう。

上述のように化学療法の対象となった腹膜転移症例の MST は，リンパ節転移や肝転移などの他の転移形式のそれに比べて短いが，その理由は腹膜転移が重症化しないと CT で確認できないことによる部分が大きいと推測される。CT 所見が明らかでない P2P3 症例の MST は7.7か月[25]と，他の転移形式の MST と大差ない。他の要因としては，腹膜転移の多くがこれまでの抗癌剤では奏効しにくい低分化型腺癌である，腹膜血管バリアーにより抗癌剤が腹腔内に到達しない，ことなどが考えられる。一方，以下の新規抗癌剤は低分化腺癌に有効性が高く，腹腔内への drug delivery が良好であることより，腹膜転移に対する治療薬として期待されている。

1．TS-1

血中 5-FU を高濃度に維持し，かつ 5-FU の用量制限毒性である消化器毒性の軽減を図るために開発された経口抗癌剤が TS-1 である。phase II試験において，低分化型腺癌に対して 52.5%と高い有効性を示し[29,30]，原発巣 C 病変に対して 20.8%と画期的な奏効率を示した[29,30]ことから，低分化型腺癌に対する有効性が示された。腹膜転移に対して有効であったとする治療成績[31-34]や症例報告[35]も数多くみられる。腹膜播種転移が完全に消失した，とする報告も散見される[36,37]。腹膜播種転移モデルを用いた動物実験では，腹水中に高濃度に 5-FU が維持されるとともに，有意な生存期間の延長がみられている[38,39]。最近，ヒト胃癌患者においても腹膜移行性が良好であることが証明された[40]。

2．Paclitaxel

本邦で行われた phase II試験で，低分化型腺癌に対して 29.0%と高い奏効率を示し注目された[41]。paclitaxel は 5-FU，CPT-11，CDDP に交差耐性を示さず，前化学療法歴を有する症例に対しても，奏効率 27%と高い有効性を認めることが特徴的である[41]。上記の報告はすべて3週間毎投与法による効果であるが，最近，薬剤投与の間隔を短くして腫瘍細胞に再増殖の時間を与えない dose-density の概念が提唱され[42]，乳癌や肺癌では weekly 投与による優れた抗腫瘍効果と毒性の軽減が報告された[43,44]。胃癌に対しても weekly 投与の有効性が報告されている[45,46]。腹水を有する腹膜転移症例に対して paclitaxel 少量分割療法が有効であったとする報告も相次いでいる[47]。また，paclitaxel は，全身投与をしても速やかに腹水中に移行し有効濃度が長期間維持されることも報告された[45]。

III．病態に応じた治療方針（図1）

肉眼的に根治切除可能な腹膜転移に対しては，2群リンパ節郭清を含めた原発巣の根治切除と播種結節の完全(R0)切除により，治癒も期待できる。R0 切除後に，日常診療では術後補助化学療法を行う場合もあるが，現在のところ有用性を示唆する evidence は乏しい。腹水細胞診陽性または腹腔洗浄細胞診陽性（CY1）で R1 切除となった症例に対しても，化学療法の有用性を示唆する evidence は乏しいが，予後が極めて不良であることより，日常診療では化学療法が行われている。JCOG では，以前に CY1 根治切除症例と P1P2 根治切除症例を対象とした手術単独群と手術＋術後化学療法群を比較する phase III試験を施行したが，症例登録が進まず試験中止となった。一方，R0 または R1 切除可能な初発腹膜転移症例に対して，術前に化学療法を行うべきか否か，明らかな evidence は乏しい。なお 2005 年の ASCO meeting で，英国 MRC 主導で行われた根治切除単独と術前化学療法＋根治切除＋術後化学療法を比較する Phase III試験の結果が報告された（MAGIC trial）[48]。術前化学療法により T，N ともに down staging が得られ，全生存期間，無病生存期間ともに試験治療群で有意な延長がみられた[48]。根治切除可能な高度進行胃癌に対して術前化学療法の有用性を示唆する evidence として注目される。

根治切除は不可能だが，原発巣の減量手術が可能である場合，前述のごとく減量手術を先行して行うべきかどうかについての evidence はない。現時点では，減量手術後に化学療法または化学療法のみを行う治療，どちらも

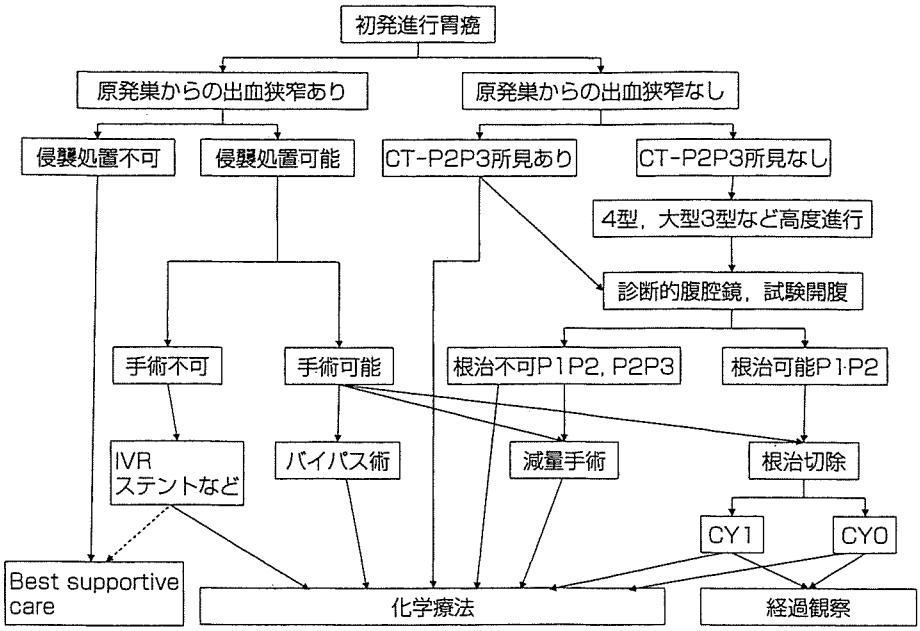

図 1 腹膜転移を有する初発胃癌の治療戦略

日常診療で行われている。しかしながら，減量手術のmortalityとmorbidityは高く食道や十二指腸への著しい浸潤を示す症例や他臓器浸潤症例で安全な減量手術が行えないと判断される場合，化学療法を選択すべきであると思われる。

原発巣に伴う出血や狭窄などが存在する場合には，出血や狭窄をコントロールするための原発巣切除やバイパス手術，stentやIVRなどが適応となる。これらの緩和的手段に伴うリスクを十分に考慮した上で，ICをとる必要がある。緩和的手段により全身状態が改善した場合は，化学療法の適応となる。

根治切除ができない場合，化学療法または緩和治療が中心となる。化学療法を行う場合どのようなregimenを用いるべきかについてはいまだ解明されていない。JCOG臨床試験のcontrol armである5-FU，試験治療群であるMTX-5-FU，低分化型腺癌に有効で腹腔内移行も良好なTS-1やpaclitaxel，あるいはこれらの薬剤を基本にしたcombinationなどが候補と考えられる。

Ⅳ．治療方針を決定するために

胃癌の腹膜播種転移ではbulky massを形成することはまれであり，CTで腫瘍所見をとらえることは困難である。腹膜転移が進行すると腹水，腸管狭窄によるイレウス，尿管狭窄による水腎症などが出現する。ある程度多量の腹水が存在する場合には，腹水細胞診によって癌細胞の有無を確認することが可能でありCY 1, Stage IVと診断できるが，腹膜播種結節が存在しているかどうかはわからない。CT所見での腹水貯留のみで“腹膜転移あり，非切除”と診断することは危険である。

腹腔鏡検査または開腹手術を行った自験例の解析では，CTで検出できる所見として腹水，腸間膜肥厚，腹膜脂肪組織のdensity上昇，結節，水腎症などがあった[25]。CTで明らかにP2あるいはP3と診断できる場合もあるが，根治切除可能かどうかを診断することは難しい。CT所見からみた腹膜転移程度診断の正確性は明らかではない。

一方，近年の化学療法の進歩により，腹膜転移が完全消失することも経験されるようになった[36,37]。遠隔転移が完全消失した場合には，根治切除術を行うchanceである。初発未治療の段階で，腹腔鏡や開腹手術により腹膜転移の程度を正確に評価しておくことは，効果判定と治療方針決定において重要と考えられる。

Ⅴ．現在，進行中または企画中の臨床試験

JCOG消化器内科グループでは，CTで明らかな腹膜転移を有する進行胃癌を対象として，5-FU単独をcontrol armとし，MTX＋5-FU療法の有用性を検証するphase III試験を実施中である。また，一次治療でfailureした腹膜転移症例を対象として，best available 5-FU (bolusとinfusionを交差させる)とpaclitaxelを比較するphase III試験を企画している。一方，JCOG胃癌外科グループでは，腹膜転移を含めた遠隔転移陽性症例を対象として，減量手術＋化学療法と化学療法単独を比較するphase III試験を企画中である。

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●原 著●

大型3型/4型/Bulky N 2進行胃癌に対するTS-1+CDDPを用いた術前化学療法の経験

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〔*Jpn J Cancer Chemother* **32**(13): 2079-2085, *December,* 2005〕

Neoadjuvant Chemotherapy Using TS-1 and CDDP against Large Type 3/Type 4/Bulky N 2 Advanced Gastric Cancer:

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Summary

This study was conducted to assess therapeutic results following neoadjuvant chemotherapy (NAC) for large type 3/type 4/Bulky N 2 advanced gastric cancer having a poor prognosis following resection. The subjects consisted of cases (≦75 y. o.) having large type 3 (diameter≧8 cm), type 4 or Bulky N 2 gastric cancer curable by resection based on preoperative imaging diagnostics. The NAC regimen consisted of TS-1 at 80-120 mg/body on days 1-21 p. o. and CDDP at 60 mg/m^2 on day 8 divided. Upon completion of two courses of 4 weeks per course, gastrectomy with≧D_2 lymphnode dissection was carried out on days 21-34. The average age of the subjects was 60.7 years, and the therapy completion rate was 80% (8/10 cases). Five of ten cases were responders diagnosed as grade 2 by histopathological examination of excised specimens (response rate 50%). Two of five responders were histopathologically evaluated as down-staging as a result of NAC (Stage IIIA → f Stage I A, Stage IV→ f Stage I A). Three of the five non-responders have relapsed, and the relapse-free interval was an average 238 days. In the five responders, one has relapsed at 331 days, while the other 4 responders have shown no relapse yet. Although NAC consisting of TS-1 and CDDP is considered to be effective against advanced gastric cancer, a phase III study with surgical treatment only will be necessary to confirm its true value. Key words: Advanced gastric cancer, Neoadjuvant chemotherapy, Down-staging (*Received Apr. 4, 2005/Accepted Jun. 21, 2005*)

要旨 【目的】大型3型(径≧8 cm) 4型胃癌，あるいはBulky N 2を有する進行胃癌に対する術前化学療法(neoadjuvant chemotherapy: NAC)の治療成績を検討した。【対象】年齢75歳以下で，術前画像診断にて根治切除可能と判断された症例を対象とした。NACのregimenはTS-1 80～120 mg/bodyを1～21日経口投与し，CDDP 60 mg/m^{2}を8日目に点滴投与し，1コース4週×2コース終了後21～34日に胃切除+D 2以上リンパ節郭清を行った。治療完遂率，手術摘出標本の病理組織学的効果判定について検討した。【結果】検討対象となった症例数は10例で，その平均年齢60.7歳，治療完遂率8/10例(80%)であり，切除標本の病理組織学的診断にてGrade 2の診断が得られたresponderは5例であり，response rateは50%であった。responder 5例のうちの2症例はNACによるdown stagingが病理組織学的に評価できた症例であり，1例はStage IIIAからStage I Aへ，別の1例はStage IVからStage I Aにdown stagingされたと推察される。non-responderの5例中3例が再発しており，そのrelapse free interval (RFI)の平均値は238日であった。一方，responderの5例中では1例が術後331日で再発を認めたが，他の4例はいまだ再発を認めていない。【結語】大型3型/4型/Bulky N 2進行胃癌に対するTS-1+CDDPのNACは有効と考えられるが，その真価を確認するために手術単独療法とのphase III studyの必要性がある。

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0385-0684/05/¥500/論文/JCLS

はじめに

近年，再発危険因子の高い腫瘍に対しneoadjuvant chemotherapy（以下NAC）が微小転移の急激な増殖を未然に防ぐ可能性が報告されている[1,2]。現在，胃癌に対する術前化学療法（以下NAC）は胃癌治療ガイドラインでは，T3，T4を対象とした臨床研究として位置付けられている[3]。切除後予後不良とされる大型3型/4型/bulky N2進行胃癌に対し，TS-1およびCDDPを用いたNACを行ってきたのでその成績を報告する。

I．対象と方法

2003年6月～2004年9月，術前診断にて大型3型（腫瘍径が8 cm以上），4型胃癌，bulky N2の進行胃癌で術前画像上根治A，Bが可能と考えられる症例を対象とし，年齢が75歳以下，performance status（PS）0～1を条件とした。10例が登録され，これらの症例に対しTS-1 80～120 mg/bodyを21日間内服投与，TS-1開始8日目にCDDP 60 mg/m²を投与した。1週間の休薬を経て2コースのTS-1＋CDDPを行った。各コース終了後にUGI，GIF，CT検査を行い増悪がないことを確認し，2コース終了後21～34日に胃切除＋D2以上リンパ節郭清を行うこととした。増悪がみられればプロトコールを中止し，直ちに手術を行うか他の化学療法に変更することとした。有害事象の判定はNCI-CTC第2版[4]に準じた。手術にて根治度A/B症例には再発が確認されるまで術後補助療法は行わなかった。手術摘出標本の病理組織学的効果判定[5]がGrade 2以上をresponder，Grade 0～1bをnon-responderとし，studyの完遂率，NAC後の組織学的効果判定について検討した。なお，本文中の用語はすべて胃癌取扱い規約第13版[5]に準じて表した。

II．結　果

1．症例の内訳（表1）

対象10症例の男女比は6：4，平均年齢60.7歳。肉眼病型では大型3型が6例で，うち1例はbulky N2を伴っていた。また4型が4例であった。

2．NACの副作用発現と手術成績（表1）

10例中2例は非完遂であった。1例（症例6）は1コース終了時の画像診断で増悪と判定されたため直ちに手術し，他の1例（症例5）は1コース目にgrade 3の食欲不振と下痢症状が出現し投与11日目で中断，2コース目はTS-1，CDDPを減量投与したが15日目でgrade 3の食欲不振が出現し中止，その後手術した。以上の結果，治療完遂率は8/10（80%）であった。NACの1，2コースを通じてgrade 3の副作用が3例（2例は食欲不振/下痢，1例は白血球減少）に出現した。RECISTガイドライン[6]による画像診断上効果判定は，PR 5例，SD 4例，PD 1例であった。手術術式は胃全摘＋D3が4例，胃全摘＋D2 5例，幽門側切除＋D3 1例であった。術後関連合併症は肝機能障害，リンパ漏，肺炎がそれぞれ1例ずつであった。在院死例はなかった。総合所見Stage ⅠA 2例，ⅠB 3例，Ⅱ1例，ⅢA 1例，Ⅳ3例であった。根治度A 5例，B 2例，C 3例であった。根治度Cの理由は，PM（＋），P1，CY1各々1例ずつであった。根治度Cでは2例にpaclitaxelを中心にした化学療法が行われた。

NACの病理組織学的効果判定がGrade 2のresponderは5例で，いずれも画像診断でPRと判定された症例であった。またSDと判定された4例のうち2例はGrade 1a，Grade 0，1bが各々1例であった。PDの1例は組織学的にはGrade 1aであった。平均観察期間は298日（136～654日）で，現在までに4例（responderの1例，non-responderの3例）に再発を認め，その平均無再発期間は238日であった。

3．Down staging症例

症例1: 65歳，女性。胃体中部の4型胃癌（図1a，b）。生検結果はsigであった。NAC 2コース終了後，画像上明らかな改善を認めた（図1c，d）。胃全摘＋脾動脈幹切除＋D2施行。摘出標本の肉眼所見では胃体中部に陥凹病変を認め（図2a），摘出標本の病理組織像はSS層まで多数の粘液結節が認められ（図2b，d），粘膜下層にわずかな癌細胞が認められるのみであった（図2c）。No 4dのリンパ節内にも粘液結節が認められ（図3a，b），No 8a，11pにも線維化がみられた（図3c，d）。病理組織学的効果判定はGrade 2であった。術後331日目にイレウスにて再手術し，大動脈周囲リンパ節転移および腹膜転移が確認されたが，PS不良のため化学療法は行えず，419日で癌死した。

症例3: 61歳，男性。噴門部の大型3型胃癌で，食道への浸潤・圧排像がみられた。生検結果はpor 1であった。NAC 2コース施行後，著しい腫瘍の縮小と食道浸潤像の消失を認めた。CT像では胃上部の壁肥厚と脾門部付近のbulky N2を認めた（図4a，b）が，NAC後，著明な縮小がみられた（図4c，d）。胃全摘＋膵体尾脾切除＋D3を行った。切除胃の病理組織学的所見では，SS層に至るまで線維化がみられ（図5a，b），食道胃接合部付近の食道および胃の粘膜下層2か所に小癌蜂巣（por 1）を認めた（図5c，d）。リンパ節組織像では11dリンパ節（図6a），16a2 latの2/12に線維化を認めた（図6b）。術後227日の現在，無再発生存中である。

表 1 TS-1+CDDP を用いた術前化学療法症例

	症例	年齢	性	生検結果	肉眼型	副作用(NCI-CTC)	臨床効果(RECIST)	手術術式	総合所見 Stage	根治度	組織学的効果判定	術後療法	再発	無再発期間	生存期間	転帰
◎	1	65	F	sig	4型	grade 1 (食思不振)	PR	胃全摘+脾動脈幹切除+D 2	I A	A	Grade 2	なし	大動脈リンパ節/腹膜	331	419	死亡
	2	47	F	tub 1 /tub 2	大型 3 型	grade 3 (白血球減少)	PR	幽門側切除+D 3	IV	B	Grade 2	なし	なし	310	310	生存
◎	3	61	M	por 2	大型 3 型 /Bulky N 2	grade 1 (口内炎)	PR	胃全摘+膵体尾脾切除+D 3	I A	A	Garde 2	なし	なし	227	227	生存
	4	72	M	tub 2	大型 3 型	grade 1 (食思不振)	PR	胃全摘+脾動脈幹切除+D 2	I B	A	Grade 2	なし	なし	205	205	生存
△	5	68	M	tub 2	大型 3 型	grade 3 (食思不振 /下痢)	PR	胃全摘+脾動脈幹切除+D 3	I B	A	Grade 2	なし	なし	147	147	生存
△	6	75	F	sig	4型	grade 2 (白血球 /血小板減少)	PD	胃全摘+脾温存+D 2	I B	C (PM+)	Grade 1 a	weekly paclitaxel	腹膜	211	654	生存
	7	50	F	por 2	4型	grade 3 (食思不振)	SD	胃全摘+脾動脈幹切除+D 2	IV	C (CY 1)	Grade 1 a	TS-1+ paclitaxel	腹壁	289	385	死亡
	8	55	M	sig	4型	grade 1 (食思不振)	SD	胃全摘+脾動脈幹切除+横行結腸+D 2	IV	C (P 1)	Gade 1 b	なし	大動脈リンパ節/腹膜	122	336	死亡
	9	56	M	por 2	大型 3 型	grade 0	SD	胃全摘+脾動脈幹切除+D 3	II	A	Grade 0	なし	なし	157	157	生存
	10	58	M	tub 1 /tub 2	大型 3 型	grade 1 (食思不振)	SD	胃全摘+脾動脈幹切除+D 3	IIIA	B	Grade 1 a	なし	なし	136	136	生存

◎: down stage 確認症例　△: 非完遂例　: responders　: nonresponders

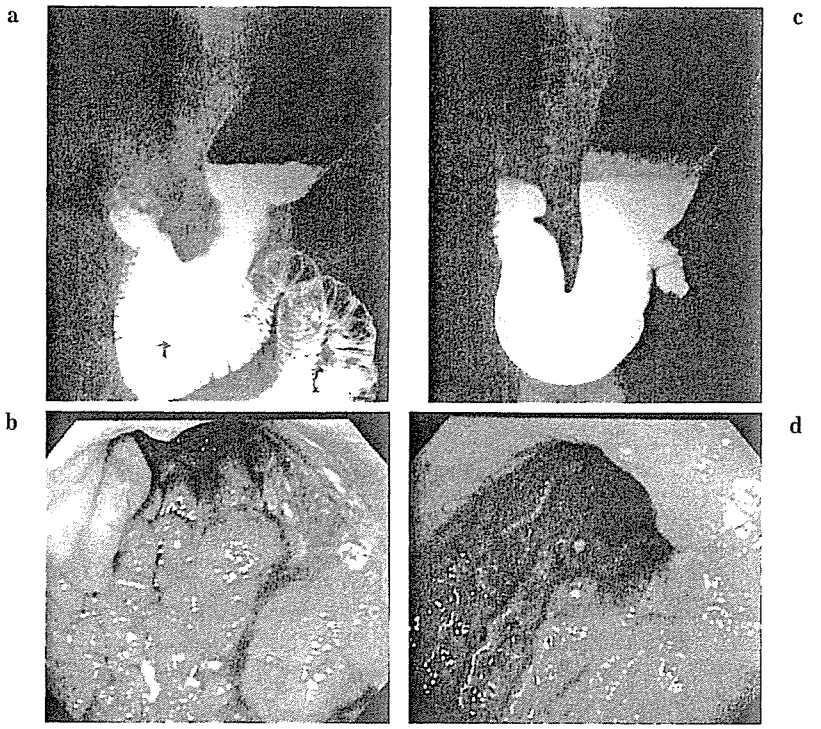

図 1 症例1の上部消化管造影，内視鏡像
a, b: 治療前
胃体中部に4型病変を認める。
c, d: 治療後
胃充盈像の胃壁の硬さは改善し，内視鏡像にて腫大皺襞の改善を認める。

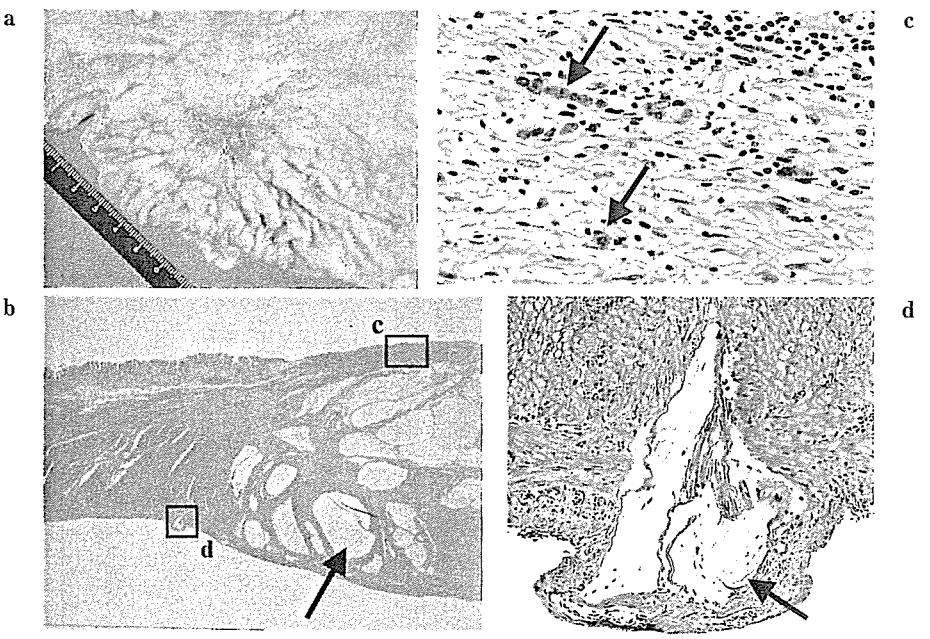

図 2 症例1の切除胃とその病理組織所見
a: 切除胃標本
胃体中部に陥凹病変を認める。
b: 切除胃ルーペ像
多数の粘液結節を認める（↑）が癌細胞の浮遊はみられない
c: 粘膜下層の病理組織像（×40）
わずかな viable と思われる癌細胞を認める（↓）。
d: 漿膜下層の病理組織像（×10）
漿膜下層にも粘液結節を認める（↑）。

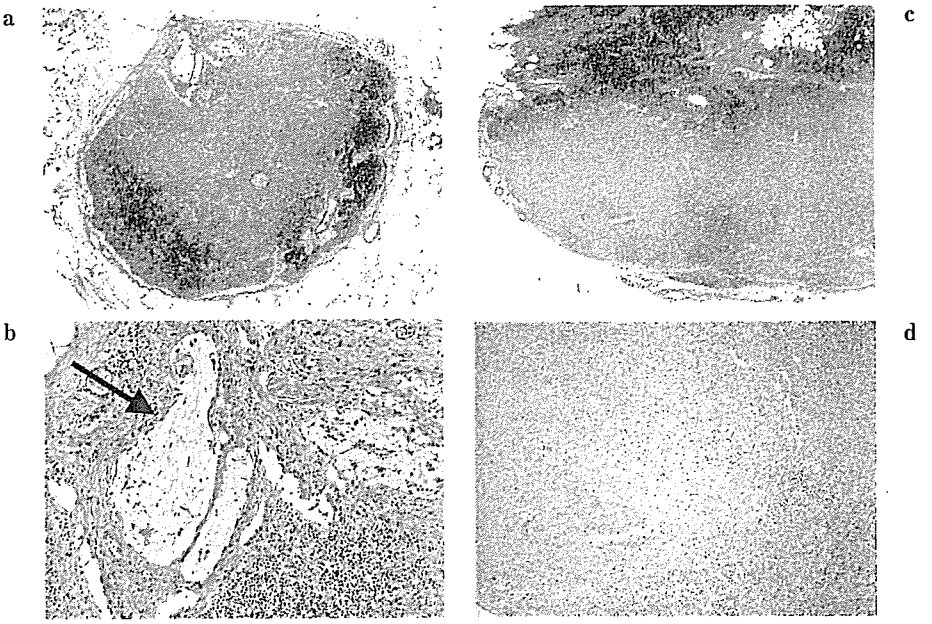

図 3　症例1のリンパ節病理組織所見
a: 4 d リンパ節のルーペ像
b: 4 d リンパ節の中拡大（×10）
　リンパ節内に粘液結節（→），線維化を認めるが癌細胞は認められない。
c: 8 a，11 p リンパ節のルーペ像
d: 8 a，11 p リンパ節の弱拡大（×4）
　リンパ節内に線維化を認めるが癌細胞は認められない。

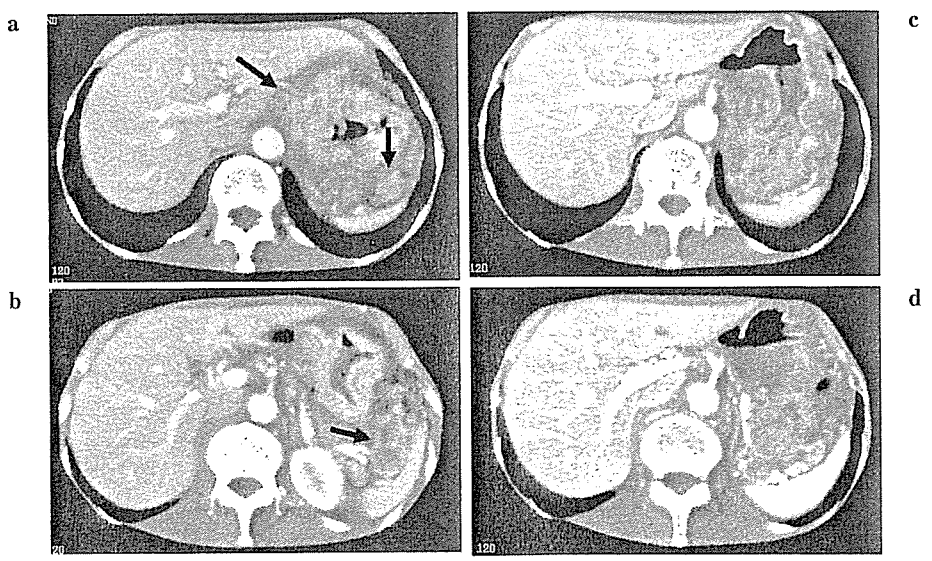

図 4　症例3の CT 像
a, b: 治療前
a: 胃上部の壁肥厚と小弯側，大弯側に一塊となったリンパ節腫大を認める（↓）。
b: 脾門部付近にも一塊となったリンパ節腫大を認める（→）。
c, d: 治療後
　著明なリンパ節腫大の消失を認める。

III. 考　　察

NAC の目的には，根治不能症例に NAC を行い down staging を図ってから根治手術しようという立場[7]と，切除可能症例に対し NAC を行い微小転移巣の根絶を目指す[1,2]二つがある。近年，胃癌に対し高い奏効率を示す抗癌剤が出現してきたことと，術後補助化学療法の効果が明らかにされていないことにより術前化学療法が注目されている[8]。進行胃癌に対する TS-1＋CDDP phase I / II　study では 76％という高い奏効率が報告されている[9]。この study は高い奏効率をもったこれら薬剤を用いた NAC により，切除予後不良な 8 cm 以上の大型3

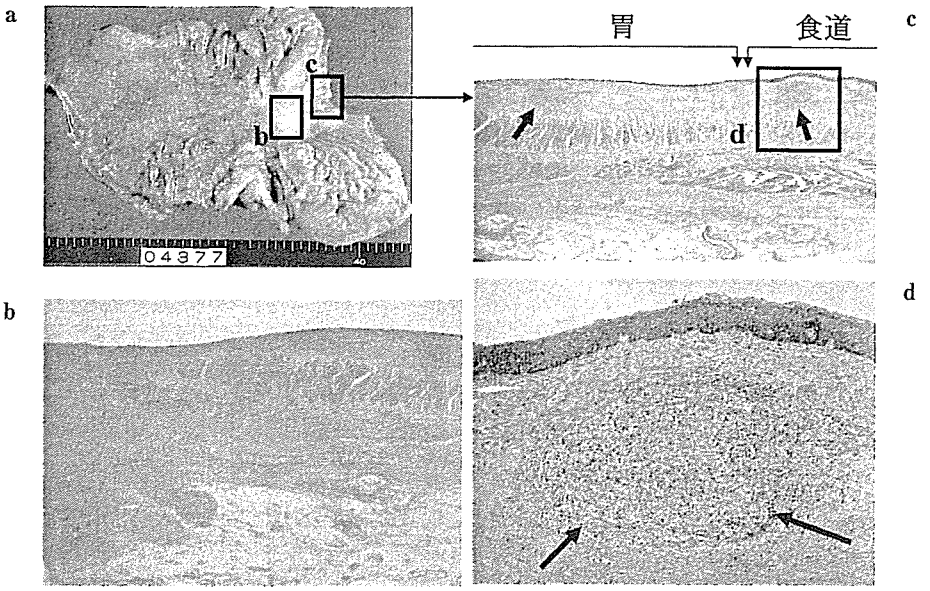

図 5 症例3の切除胃標本とその病理組織所見
a: 切除胃標本
b: 胃壁のルーペ像
病巣が存在したと思われる胃壁はSS層に至るまで線維化がみられる。
c: 食道胃接合部付近に食道および胃粘膜下層の2か所に小癌蜂巣を認める（↑）。
d: 食道壁の病理組織像中拡大（×10）
por 1病変の残存（↑）。

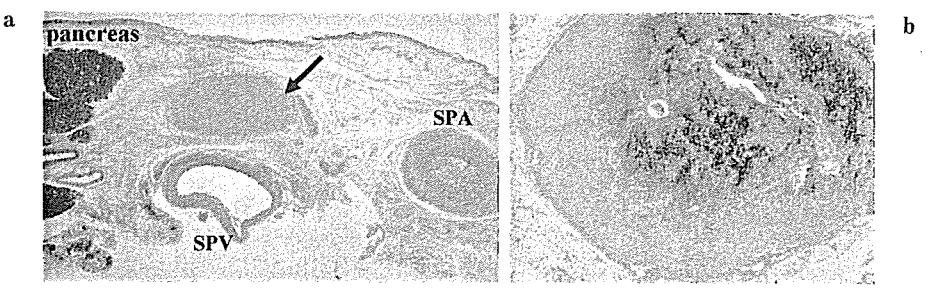

図 6 症例3のリンパ節病理組織所見
a: 膵尾部切片のルーペ像
11dリンパ節が線維化し癌細胞が認められない（↓）。
（SPV: 脾静脈，SPA: 脾動脈）
b: 16a2 latのルーペ像
2/12に線維化を認める。

型[8]，4型胃癌[8]およびBulky N2胃癌[10,11]の予後改善を期待して行われた。regimenはJapan Clinical Oncology Group（JCOG）の胃がん外科グループによるTS-1＋CDDPを用いた術前化学療法のstudy（JCOG-0210）に準じた。

TS-1＋CDDP療法は高い有効性を示す反面，毒性も強いことが予想される。薬物毒性のためNAC後の手術療法が行えなくなることを懸念し，NACは2コースと設定した。また，NACの有効性をより明確にしたいという目的で，根治度A・B症例には術後補助化学療法は再発が確認されるまで行わないこととした。

NACの利点として薬剤効果が組織学的に評価できることがあげられている[12]。藪崎ら[13]は根治不能と診断された37例にTS-1＋CDDPのNACを行い臨床診断にて62.2%の高い奏効率を報告しているが，切除された24例のうち組織学的効果判定でGrade 2が得られた症例は6例（25%）にすぎない。われわれの検討は，病理組織学的効果Grade 2をresponderとして評価した。その結果5例（10例中）のresponderが得られた。それらはいずれもRECIST[6]による画像効果判定でもPRという評価が得られた症例であった。

このstudyでは切除可能症例を対象にNACを行ってきたが，その問題点として化学療法無効例に手術時機を逸する可能性があげられる。症例6のように，NACの効果はPDで，術後再発を来したものの術後paclitaxelのweekly投与に変更し，長期生存している症例もあるの

でNAC施行中，画像上増悪と診断される症例には早期にregimenを変更するか，術後薬剤を変更したadjuvant chemotherapyを考慮すべきと思われる。また，4例の再発例がいずれも4型の胃癌であることは，4型胃癌に対しては2コース以上のNACを行うか，術後補助化学療法の必要性を示唆している可能性がある。

組織学的見地からNACによるdown stagingが得られたと思われる症例がresponder 5例中2例に認められた。症例1は治療前T2 (SS)，N2 Stage IIIAからpT1 (SM)，pN0，CY0，sP0，sH0 Stage IAに，症例3は治療前T2(SS)，N3 Stage IVからpT1(SM)，pN0，CY0，sP0，sH0 Stage IAにdown stagingされた症例と推察される。

NACが術後の生存期間に貢献できるかどうかについてはいくつかの報告があり[7,14,15]，responderの生存率は高い[7,15]という報告もみられるが，いまだNACが術後予後改善につながる明確なエビデンスは得られていない。今後，切除可能進行胃癌を対象として多施設共同研究によるNAC+surgeryとsurgery aloneとの第III相試験による客観的評価の必要性がある。

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World J. Surg. 29, 1131–1134 (2005)
DOI: 10.1007/s00268-005-7703-6

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When Is Curative Gastrectomy Justified for Gastric Cancer with Positive Peritoneal Lavage Cytology but Negative Macroscopic Peritoneal Implant?

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Published Online: August 11, 2005

Abstract. For gastric cancer patients who have no peritoneal seeding at a macroscopic level but positive results in the peritoneal lavage cytology (PLC), the prognostic benefit expected by surgical resection is still controversial. During the period 1975–1994 as series of 417 consecutive patients without distant organ metastases underwent surgical resection for gastric cancer that had invaded the subserosal or deeper layers of the stomach wall. Immediately after laparotomy, the pouch of Douglas was washed with 100 ml of physiologic saline solution, and the fluid was collected for cytologic examination (four slide glasses) using Giemsa and Papanicolaou staining methods. According to the macroscopic (P) and cytologic (Cyt) results, the 417 patients were classified into three groups: P^+ ($n = 97$); P^-/Cyt^+ ($n = 25$); and P^-/Cyt^- ($n = 295$). Their 3-year survival rates after surgical resection were 4%, 24%, and 48%, respectively ($p = 0.0001$: P^-/Cyt^+ vs. P^-/Cyt^-; $p = 0.0018$: P^-/Cyt^+ vs. P^+. Among the 25 P^-/Cyt^+ patients, postoperative survival was not associated with the T stage, N stage, cellular atypism, or cluster formation but with the number of cancer cells per slide during PLC. The 3-year survival rate was 35% for the subgroup with fewer than 10 cancer cells per slide (17 patients) and 0% for the other subgroup with 10 or more cancer cells per slide (8 patients) ($p = 0.017$). For P^-/Cyt^+ patients, who represent a subgroup of gastric cancer patients with an intermediate survival rate between the P^-/Cyt^- and P^+ patients, the number of cancer cells observed during PLC offers a potent prognostic indicator for the gastrectomy.

Despite the recent spread of gastroscopic examinations, a large number of gastric cancers are diagnosed in advanced stages. Once the primary tumors invade directly into the subserosal or serosal layers of the gastric wall, cancer cells are more likely to spread into the abdominal cavity and consequently implant on the peritoneal surface (peritoneal dissemination) [1]. At present, when peritoneal implants at a macroscopic level (implant-positive, or P^+) are detected during laparotomy, it is generally accepted that gastrectomy does not provide a prognostic benefit for them. Even after a curative gastrectomy is performed for those who have no peritoneal seeding at a macroscopic level (implant-negative, or P^-), peritoneal dissemination is the most common cause of subsequent cancer death [2–4]. Thus, some authors have tried to detect occult peritoneal dissemination using peritoneal lavage cytology (PLC) for stricter indications of the curative gastrectomy [5, 10–10]. Although P^- patients with negative PLC (Cyt^-) resulted in far better long-term outcomes after resection than P^- patients with positive PLC (Cyt^+) [11, 12], it is still controversial whether curative gastrectomy should be abandoned for all P^-/Cyt^+ patients. It is of no doubt that the floating cancer cells in the peritoneal cavity do not always survive to form an implantation. Boku et al. reported that the 3-year survival rate after gastrectomy was 25% in P^-/Cyt^+ patients [11], but they did not mention any shared characteristics of this survival group.

Among Cyt^+ patients, there is wide variation in the number of cancer cells detected, the presence or absence of cluster formation, and the degree of cellular atypism. In reviewing the previous reports, only cluster formation was once taken into consideration by a small number of authors, but no definitive conclusions have yet been determined in association with patient survival [7, 13]. Thus, the present study was conducted to clarify whether curative gastrectomy should be abandoned for all P^-/Cyt^+ patients from the viewpoint of long-term outcome (by analyzing more detailed cytologic features).

Patients and Methods

During 1975–1994, a series of 417 consecutive patients underwent surgical resection with curative intent of gastric cancers that had invaded the subserosal or deeper layers of the stomach wall, at The Osaka Medical Center for Cancer and Cardiovascular Diseases. This group of patients included a number of cancer patients

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in whom macroscopic curative resection was considered possible, regardless of the presence of peritoneal implants. However, patients were excluded from the study when at the preoperative workup (laparoscopic staging) or at laparotomy numerous macroscopic peritoneal implants to distant peritoneum were found or when massive lymph node metastases beyond the surgical field or liver metastases were revealed. All patients whose resection was abandoned died within 2 years after laparotomy.

When such types of cancer extension were not proven, the peritoneal cavity was washed with 100 ml of physiologic saline solution (37°C), and the fluid was then collected from the pouch of Douglas. The collected fluid was immediately centrifuged at 2000 rpm for 3 minutes, and the sediment was smeared on four slide glasses. The slides were stained by Giemsa and Papanicolaou methods and diagnosed by cytologists who were blinded to the clinical information [14]. The PLC results were classified as positive when at least one cancer cell was detected; a suspicion of malignancy was classified as negative. The diagnosis of a cancer cell was based on nuclear size including the nuclear/cytoplasm (N/C) ratio, its anisokaryosis, membrane pattern, nucleoli pattern, and density of chromatin. Postoperatively, for the cytology-positive slides, the total numbers of cancer cells were counted, and the presence or absence of cluster formation of cancer cells was determined. The detected cancer cells were also examined as to whether they had severe nuclear atypism showing a high N/C ratio and dense chromatin (Fig. 1) [15–17]. In the gastrectomy cases, the distal two-thirds of the stomach or the entire stomach was removed, and a regional lymphadenectomy was done. Before closing the abdomen, the intraperitoneal space was washed with 2000 ml of physiologic saline.

After surgery, patients were followed at our outpatient clinic with an interval of 3 to 6 months, including physical checkups and laboratory examination of tumor markers such as the carcinoembryonic antigen (CEA). In addition, chest roentogenography, gastric endoscopy, and abdominal ultrasonography and computed tomography (CT) were performed to determine if tumor recurrence was present. If present, the site(s) were also determined.

Patient survival was calculated by means of the Kaplan-Meier method, and the statistical significance of the differences between curves was tested by the log-rank test. Significance was assumed if $p < 0.05$. The statistical analyses were performed using the StatView 5.0 program (SAS Institute, Cary, NC, USA).

Results

The 417 patients who had undergone surgical resection consisted of 256 men and 161 women with a mean age of 60 ± 12 years (range 27–87 years; median 61 years). According to both P and Cyt results, they were classified into the following three groups: P^+ ($n = 97$); P^-/Cyt^+ ($n = 25$); and P^-/Cyt^- ($n = 295$). Figure 2 shows the postoperative survival rates of these three groups. The 3-year survival rates after surgical resection were 4%, 24%, and 48%, respectively ($p = 0.0001$: P^-/Cyt^+ vs. P^-/Cyt^-; $p = 0.0018$: P^-/Cyt^+ vs. P^+). The median survival periods were 10.8, 18.4, and 30.0 months, respectively. The groups showed similar patterns in that most of deaths occurred within 30 postoperative months but were rare thereafter.

Among the 25 P^-/Cyt^+ patients, 17 patients died within 30 postoperative months (2.5 years) and 8 patients survived 30 months or more. Excluding one patient who is still alive at 5 years and another patient who died of other disease (noncancer), the other 23 patients died of cancer. The cause of cancer death was peritoneal dissemination in 19 patients (79%); liver metastases, lung metastases, and pleuritis carcinomatosa were seen in one patient each. Table 1 compares the background factors between the two subgroups, which were classified according to whether patients survived more than 30 postoperative months or not. As a result, age, gender, the depth of cancer invasion in the gastric wall, the status of nodal involvement (UICC classification), or the histologic type of cancer did not differ between the two subgroups.

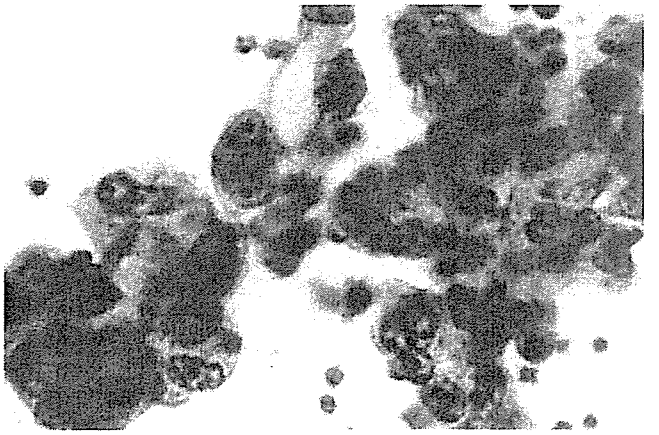

Fig. 1. Severe cellular atypism showing higher N/C ratio and dense chromatin. (Papanicolaou staining of intraperitoneal free cancer cells, ×40).

Importantly, the number of cancer cells per slide differed significantly ($p = 0.019$). Ten or more cancer cells were detected in 8 (47%) of 17 patients who died within 30 months but in none of the 30-month survivors. However, neither cluster formation nor severe nuclear atypism reached statistical significance. Figure 3 compares patient survival in association with the number of cancer cells. The 3-year survival was 35% in 17 patients with fewer than 10 cancer cells per slide, which was significantly better than 0% in the 8 patients with 10 or more cancer cells per slide ($p = 0.017$). The median survivals were 25.5 and 8.6 months, respectively. The latter subgroup had survival rates similar to those of the P^+ patients ($p = 0.96$) (Fig. 3).

Discussion

The fluid collected from the peritoneal washing contained not only exfoliated cancer cells but also mesothelial cells, histiocytes, and other nonmalignant cells. Floating cancer cells usually show a wide variety of degeneration. A strict definition was applied to the cancer cells that excluded suspicious or borderline malignant cells because we had previously considered it necessary not to overlook any candidates for longer-term survival during the gastrectomy. As a result, only 25 (8%) of 320 P^- patients showed positive cytology results despite direct invasion of their primary gastric cancers to the subserosal or deeper layers of the wall of the stomach. Likewise, among our 97 P^+ patients, the Cyt^+ rate was also low: 56% (54 patients). Similarly, Bonenkamp et al., with a

Table 1. Clinicopathologic characteristics of P^-/Cyt^+ patients (n = 25) with respect to survival after surgery.

Survival after surgery years	No. of patients, by years of survival after surgery		p
Parameter	≥ 30 months	< 30 months	
No. of Patients	8	17	
Age (years)	53.1 ± 12.3	62.3 ± 11.4	
Gender			0.48
Male	4	11	
Female	4	6	
Surgical resection			0.40
Distal gastrectomy	2	2	
Total gastrectomy	6	15	
Depth of tumor invasion			0.54
T2	4	6	
T3	4	9	
T4	0	2	
Lymph node involvement (UICC)			0.21
N1	4	3	
N2	1	6	
N3	3	8	
Histology			0.82
Differentiated	2	5	
Undifferentiated	6	12	
No. of cancer cells per slide			0.019
< 10	8	9	
≥10	0	8	
Cluster of cancer cells			0.94
Absent	2	4	
Present	6	13	
Large cancer cells with severe cellular atypism			0.054
Absent	8	11	
Present	0	6	
Major cause of death[a]			0.61
Peritoneal dissemination	6	13	
Other	1	4	

[a]Except for one patient who survived more than 5 years and is still alive.

strict definition like ours, showed that the sensitivity rate of PLC was as low as 28% to 60% [12]. Thus, we consider that no false-positive cases were included among our 25 Cyt^+/P^- patients.

In the present result, the P^-/Cyt^+ group showed an intermediate survival rate between the P^-/Cyt^- and P^+ groups (Fig. 2). Because similar results were reported by Boku et al. [11] and Bonenkamp et al. [12], it raises the question of whether a survival benefit would be gained by gastrectomy among P^-/Cyt^+ patients. Although both T and N stages are generally accepted as simple, potent indicators in cancer staging, all of our 25 P^-/Cyt^+ patients had both nodal involvement and T2 or more depth of cancer invasion. Thus, instead of N or T stages, some other prognostic indicators should be applied to such a limited group of P^-/Cyt^+ patients.

The present report seems to be the first to compare three cytologic features (number of cancer cells, cellular atypism, and cluster formation) in association with patient survival. It concluded that the number of cancer cells was the only significant prognostic factor (Table 1, Fig. 3). The survival curve in the subgroup with 10 or more cancer cells was similar to that of the P^+ group, and the survival curve in the subgroup with fewer than 10 cancer cells was similar with that of the P^-/Cyt^- group during the first 30 postoperative months (Fig. 3). Such a clear association with the number of cancer cells seems to be partly explained by the fact that the cancer cells were counted objectively, whereas the definition of cellular atypism is subjective, with a wide variation among cytologists.

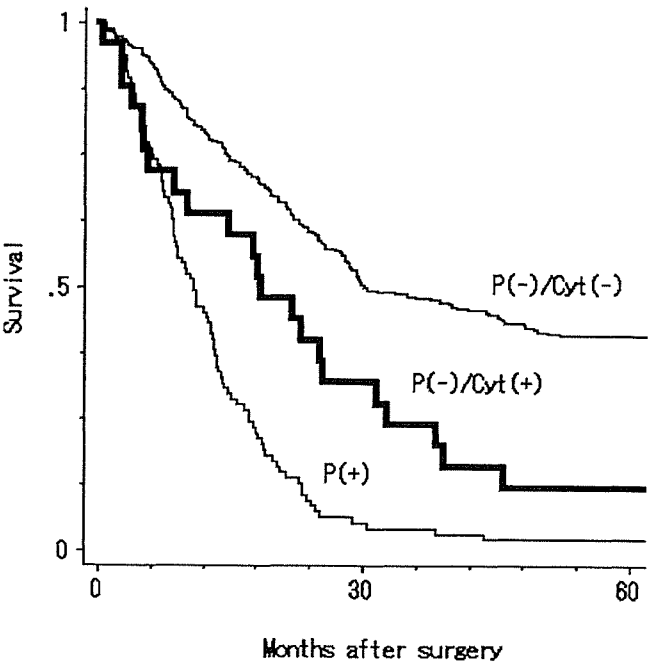

Fig. 2. Survival curves for patients with gastric cancer that invaded the subserosal or deeper layers with respect to peritoneal implants at a macroscopic level (P) and peritoneal lavage cytology (Cyt) results: P^+ (n = 97); P^-/Cyt^+ (n = 25); and P^-/Cyt^- (n = 295). (p = 0.0001 for P^-/Cyt^+ vs. P^-/Cyt^-. p = 0.0018 for P^-/Cyt^+ vs. P^+.

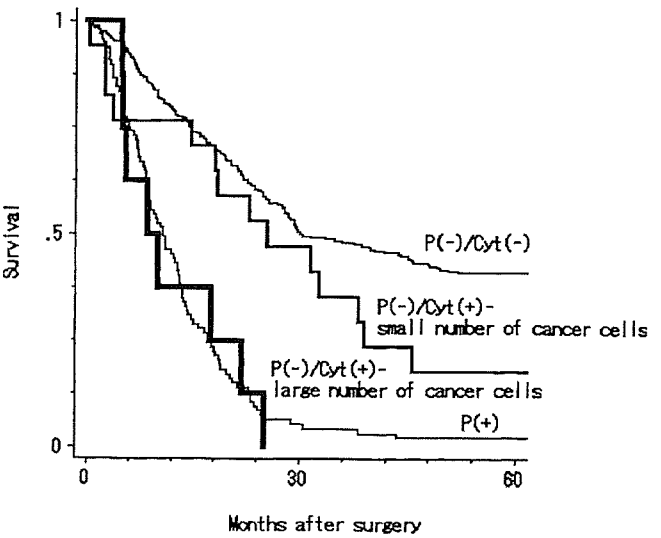

Fig. 3. Survival curves for P^-/Cyt^+ patients in association with the number of cancer cells. p = 0.017 for 8 patients with a large number of cancer cells by peritoneal lavage cytology (PLC) versus the 17 remaining patients. Survival curves did not differ significantly between the subgroup of patients with large numbers of cancer cells in the P^-/Cyt^+ group and the P^+ patients (p = 0.96).

Regarding cluster formation, an experimental study suggested that the up-regulation of adhesion molecules on cancer cells, which might be related to the clustering tendencies of cells, prevents apoptosis in vitro [18]. However, Majima et al. [13] suggested that cluster formation was of poorer prognosis, whereas Iitsuka et al. [7] reported that clusters were associated with a better prognosis. Considering that the presence or absence of cluster formation is easily judged by the microscopic observation itself, their opposite conclusions might have been partly due to artifacts (cell aggregation) that appeared during the cell treatment procedures.

Our classification based on the number of cancer cells is simple and requires no additional time-consuming procedure. In other words, it is practical for surgical decision-making, especially for laparoscopic staging, which is often applied to patients with gastric cancers that invaded the submucosal or deeper layers.

In this retrospective series, the P^-/Cyt^+ patients accounted for only 6% (25/417), and 23 of 25 patients underwent some postoperative chemotherapy. Whereas we recognize the possibility that these factors may have some impact on selection bias or outcome in the study and the importance of verification by further studies, newer therapies are needed for this subgroup. Our classification based on the number of cancer cells would be helpful for selecting the candidates more appropriately.

Although our subgroup with a small number (< 10) of cancer cells survived longer after gastrectomy than the other subgroup (≥ 10), 6 of 8 patients in the former subgroup finally died of peritoneal dissemination. When gastrectomy is applied to patients in the low cancer cell number subgroup, some adjuvant therapies, specifically focused on peritoneal dissemination, are needed. Some recent authors reported a few successful cases in which carcinoma of the peritoneum disappeared after chemotherapy [19]. Studies are also required to confirm which anticancer drug is most effective for controlling peritoneal dissemination.

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Original article

Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial

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Background: Extended lymphadenectomy (D2) provides accurate nodal staging of gastric cancer. The aim of this study was to clarify the degree of stage migration seen with D2 combined with para-aortic lymph node dissection for gastric cancer invading the subserosa, the serosa and adjacent structures (T2ss–4) in patients considered not to have distant metastases (M0).

Methods: Between July 1995 and April 2001, 523 patients were recruited and randomized in a prospective phase III trial comparing D2 with D2 and para-aortic nodal dissection for T2ss–4 gastric cancer without macroscopic para-aortic nodal metastases. Stage migration was evaluated by Japanese Gastric Cancer Association staging in 260 patients who underwent D2 with para-aortic dissection by analysing pathological information from the dissected lymph nodes.

Results: Node (N)-stage migration was observed in 1 per cent (1 of 82) of patients with N1 disease, 20 per cent (12 of 59) with N2, 43 per cent (10 of 23) with N3 and 8·8 per cent (23 of 260) of all patients. Final stage migration occurred in 9 per cent (5 of 58) of patients with stage IIIa, 19 per cent (8 of 42) with stage IIIb, 56 per cent (9 of 16) with stage IVa and 8·5 per cent (22 of 260) of all patients. Metastasis to N4 nodes was found in 4 per cent (four of 95) of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. The overall incidence of N4 involvement was 8·8 per cent (23 of 260).

Conclusion: Extended para-aortic lymphadenectomy for gastric cancer provides accurate nodal staging and results in stage migration, which may improve stage-specific survival regardless of overall survival benefit.

Paper accepted 27 September 2006

Published online 19 October 2006 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.5487

Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most common malignancy in Japan, South America and Eastern Europe[1]. Radical gastrectomy with regional lymphadenectomy is the mainstay of curative treatment for gastric cancer that has penetrated beyond the submucosa[2]. The procedure can be undertaken in the context of total or subtotal gastrectomy where (D2) lymphadenectomy indicates nodal dissection to the N2 level[3]. This has been the standard treatment for gastric cancer in Japan since the 1960s[4].

In the 1980s extended lymphadenectomy procedures were practised in many Japanese centres with the intention of improving the prognosis of patients with locally

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

advanced gastric cancer. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected on the basis that 20–30 per cent of patients with non-early gastric cancer (more than T1) had microscopic metastasis present in para-aortic nodes[5–8]. The reported 5-year survival rate for patients with these nodal metastases was in the range of 14–30 per cent after extended para-aortic lymphadenectomy[5–9].

Based on these results, the Japanese Gastric Cancer Association defined para-aortic nodes as regional lymph nodes[10]. Conversely, the International Union Against Cancer (UICC)–tumour node metastasis (TNM) system classified metastases to para-aortic lymph nodes not as regional lymph node metastases (N) but as distant metastases (M)[11]. Keighley *et al.*[12] reported that median survival was less than 5 months in British patients with tumours involving para-aortic nodes, even after extended para-aortic nodal dissection.

From retrospective studies, it has been suggested that extended para-aortic lymphadenectomy improved prognosis compared with standard D2 dissection[9,13]. It may be, however, that extended surgery only provides more accurate staging information and that this stage migration may improve apparent stage- and N stage-specific survival[14]. The impact of stage migration has not yet been clarified.

A multi-institutional randomized clinical trial was therefore conducted by the Japan Clinical Oncology Group (JCOG) to evaluate the survival benefit of D2 gastrectomy with extended para-aortic dissection for T2ss–4 M0 gastric cancer (ss, subserosal) without macroscopic para-aortic nodal metastases. Morbidity and mortality results from this trial showed that D2 as well as extended surgery could be performed safely in specialized hospitals in Japan[15]. The present report evaluated the stage migration caused by D2 with para-aortic lymphadenectomy by analysing pathological information from dissected lymph nodes in this prospective trial. This is the first study to evaluate stage migration caused by para-aortic dissection.

Patients and methods

The randomized trial[15] was approved by the JCOG and the local ethics committees of each institution. Initially, the 12 institutions of the Gastric Cancer Surgery Study Group of the JCOG participated in the trial, followed by 12 additional institutions to increase recruitment. All data management and quality assurance were done by the JCOG data centre.

Between July 1995 and April 2001, 523 patients with T2ss–4 M0 tumours, without gross metastases in para-aortic nodes, were randomly assigned to D2 (263 patients) or D2 with para-aortic dissection with curative intent (260). Para-aortic lymph nodes of 1 cm in diameter or larger were diagnosed as metastases by computed tomography. After mobilization of the duodenum, nodal status was finally judged by palpation. The effects of stage migration were evaluated in the 260 patients who underwent D2 with para-aortic lymphadenectomy.

The 12th edition of the Japanese Gastric Cancer Association staging system was used[10]. Lymph nodes were divided to four groups: group 1 or N1 consisted of the perigastric nodes along the lesser curvature (stations 1, 3 and 5) and the greater curvature (stations 2, 4 and 6); group 2 or N2 consisted of the nodes along the left gastric artery (station 7), along the common hepatic artery (station 8), around the coeliac artery (station 9) and along the splenic artery (stations 10 and 11); group 3 or N3 consisted of nodes along the hepatoduodenal ligament (station 12), around the pancreas (stations 13, 15, 17 and 18) and along the superior mesenteric vein (station 14); and group 4 or N4 consisted of para-aortic lymph nodes (station 16). D2 dissection involved removal of all N1 and N2 nodes for tumours in the proximal and middle stomach, and additionally stations 12, 13 and 14 for tumours in the distal stomach. For D2 with para-aortic dissection, the para-aortic lymph nodes were removed in addition to the D2 dissection. Quality control concerning nodal dissection has been described; the median number of retrieved nodes was 54 (range 14–161) in D2 and 74 (range 30–235) in D2 with para-aortic dissection[15].

The lymph nodes of each station were retrieved individually from the specimen and numbered according to the Japanese Gastric Cancer Association staging system. The stomach and lymph nodes were stained with haematoxylin and eosin for histopathological examination.

Stage migration was calculated by assuming that patients had undergone hypothetical D2 dissection without para-aortic lymphadenectomy. Lymph nodes were staged according to the N1, N2 and N3 status, without N4 information (standard staging). Restaging was then undertaken after considering N4 status obtained by true extended para-aortic lymphadenectomy (extended staging). In this way, N-status migration could be determined when metastatic nodes were detected in the N4 levels. A final stage was determined in both the standard and extended staging by combining microscopic depth of invasion into the gastric wall (T status).