標準的治療の確立と臨床試験

標準的治療法の確立には臨床試験としてランダム化比較試験（Randomized Controlled Trial; RCT）によるエビデンスが必要不可欠である．がん治療を担当しているどの位の医師が「臨床試験とは何か」を理解できているであろうか．**「臨床試験」とは，ある疾患に対する有効かつ安全な治療法を確立するため，ヒトを対象として行われる科学的かつ倫理性を持った医学研究**である．一般的に，がんに対する臨床試験の流れを簡単にまとめると，非臨床試験（培養がん細胞→動物実験）を通して有望な薬剤はヒトでの臨床試験へと移行する．Phase Ⅰ study（最大耐容量：MTDや推奨用量の決定）結果に基づき，phase Ⅱ studyにて，対象がん腫に対する効果（奏効率）・毒性が評価される．これで有用性があると判断されるとphase Ⅲ studyとして，有効性および安全性からみた総合評価において既存の治療法との比較（ランダム化）が行われ，これを上回れば新しい標準的治療として確立されることになる．このためには適切な症例登録が行われ，迅速に質の高いデータを解析し，正しく有効性と安全性に関する情報が把握できねばならない．

米国の臨床研究体制からみたわが国の後進性

1．米国での研究体制（組織）

米国では政府の下，Department of Health & Human Service（DHHS）があり，その傘下のひとつにFood & Drug Administration（FDA）やNational Institute of Health（NIH）などの多くの組織があり，NIHの下部組織としてがんに対する専門機関National Cancer Institute（NCI）が機能している．NCIは国内のがん研究費を一元管理し，研究者の登録や資格剝奪の権利も有している．同時に，NCIは自らFDAに治験届けを提出し，独自に新薬開発（phase Ⅰ/Ⅱ study）を行うこともでき，有望な薬剤は製薬企業に無償提供され，製薬企業は引き続きphase Ⅲ studyを行う（例：paclitaxel）．時間とともにコスト削減が可能となり，国益を掲げた取り組みが展開される．NCIがスポンサーとなる臨床試験はこの一部門であるCancer Therapy Evaluation Program（CTEP）によるプロトコール審査承認や監査監視を通じてGOGなどの多施設共同研究グループのみならず，全米各地のがんセンターでの試験もすべて掌握されている．GOG-JapanとしてGOG Studyに登録するには，個人・施設ともこれら数多くの部署の認可を得るための膨大な資料作成とそれに基づき承認を得ることが必要になる（詳細は，「Ⅰ．欧米の臨床研究グループに学ぶ　2．GOG」を参照）．また，倫理面はより厳しく，すべての試験，すべての施設IRBはOffice for Human Research Protections（DHHS-OHRP）の監視下にある．当然，GOG-Japan参加施設IRBはこの基準を満たしたうえでDHHS-OHRPの審査を受け，毎年亢進せねばならない．これに対して，厚生労働省健康局国立病院部政策医療課が管理する特別予算「がん研究助成金」を基盤に運営されるJCOGでさえ，計画されている試験や行われている試験を全般的に把握し管理する国家機関はまったく存在しない．以上，いかに日本が野放し状態で臨床試験もどきの治療が行われているかを認識すると同時に臨床試験への正しい理解と行う際の責任の大きさを理解していただければと思う．

2．臨床試験の法的・財政的基盤

米国では上記のシステム下ですべての臨床試験は連邦法により法的規制を受けているのに対し，日本では厚生労働省令28号でGCP（Good

Clinical Practice) として治験と市販後臨床試験のみがチェックされているにすぎない．研究倫理は米国では上述のようにDHHS-OHRPが睨みをきかせているが，日本では治験や市販後臨床試験以外は何ら規制がなく，われわれはそれぞれ「ヘルシンキ宣言」を遵守しているというしかない．資金面でも多くの問題がある．JCOGは公的研究費「がん研究助成金」を基盤に試験が遂行されるが，JGOGはNPO組織として会員会費や製薬関連企業の寄付により独自に試験を行っている．いずれにせよ，臨床試験によって医療機関にもたらされる実感できる財政的メリットはないに等しい．米国では公的研究費で研究に要するすべての経費がカバーでき，研究者自身やスタッフ（CRCやResearch Nurse）の給料を各施設で自由に運用できる．わが国での公的研究費（助成金・補助金）の配分は限定されるうえに，人件費としての使用はできない．間接経費もやっと認められたが（平成13年度より），ほとんど行われていない5,000万円/年以上の厚生科学研究に限られている．

さらに，わが国では医師主導臨床試験など公的・自主的研究では，よく議論になる補償制度の完備もなく，医療機関は公的・自主的研究を行うリスクも有する（受託研究は補償制度があり施設への収入もある）．この状況が続く限り，欧米と肩を並べて標準的治療法を作る側には立てないだろう．

以上，批判的記述をおこなったが，標準的治療を決定する臨床試験に対する国の取り組み（体制・研究費）が決定的に遅れていることが第一の大きな問題点であることが理解できる．厚生労働省内ではこの現実に危惧を抱いている多くの方々がいるが，個々のレベルでは縦割りの壁を越えられず，トップクラスの理解と強いリーダーシップが必要であろう．

臨床試験に必要なinfrastructure

いざ，臨床試験を実施するには，「組織・人・金」の3要素が必要となる（**図1**）．臨床試験を科学的かつ倫理的に行うためには，試験の主体となる臨床研究者グループ，データ管理・統計解析を行う支援機構としてのデータセンターおよび第3者的監視機構として倫理委員会やモニタリング委員会の3要素から構成される組織が重要なインフラである．この組織を動かすには国や製薬企業からの莫大なお金が必要不可欠となる（**図1**）．以上のすべての体制においてわが国は大きな問題点（研究者からみればハンデイ）を抱えている．欧米（とくに米国）では1950年代からこの体制作りが脈々と堅固に進められてきた．しかし，わが国ではこの体制作りも決定的に立ち遅れている．どうも日本人は個々の能力では劣らないが，system organizationは苦手なようで，まず，欧米にその体制を学んで，それに準じた組織を立ち上げ，将来は欧米と対等に臨床試験が行えるようにできることを目指すことが現時点でもっとも早道と考えられる．JGOGの中のひとつの委員会であるGOG-Japanはその主旨で立ち上げられ（**図2**），種々の困難を乗り越えて，現在13施設で構成され，GOG studyに約90例の症例を登録し，GOG Auditも通過できた．さらに，GOGプロトコールの提案，GOG studyのchart reviewも担当している（GOG 182）．GOGから症例ごとに支払われる登録料からtravel expenseとしてGOG business meetingの参加委員の旅費を出している．近い将来，わが国での体制作りに大きな力となると考えられる．

以下，臨床試験の3要素についてみてみる（**図1**）．

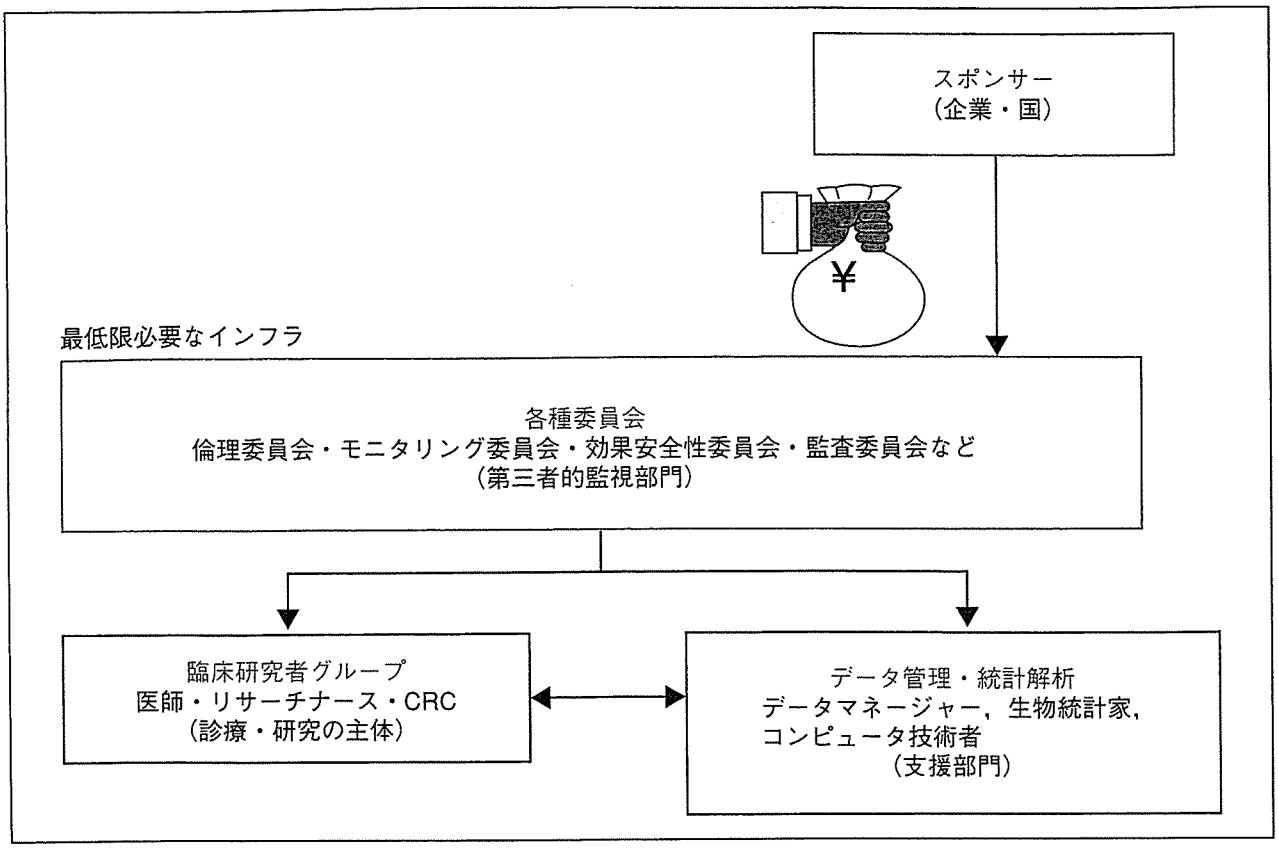

図1　臨床試験：必要な組織（国立がんセンター情報研究部　福田治彦）

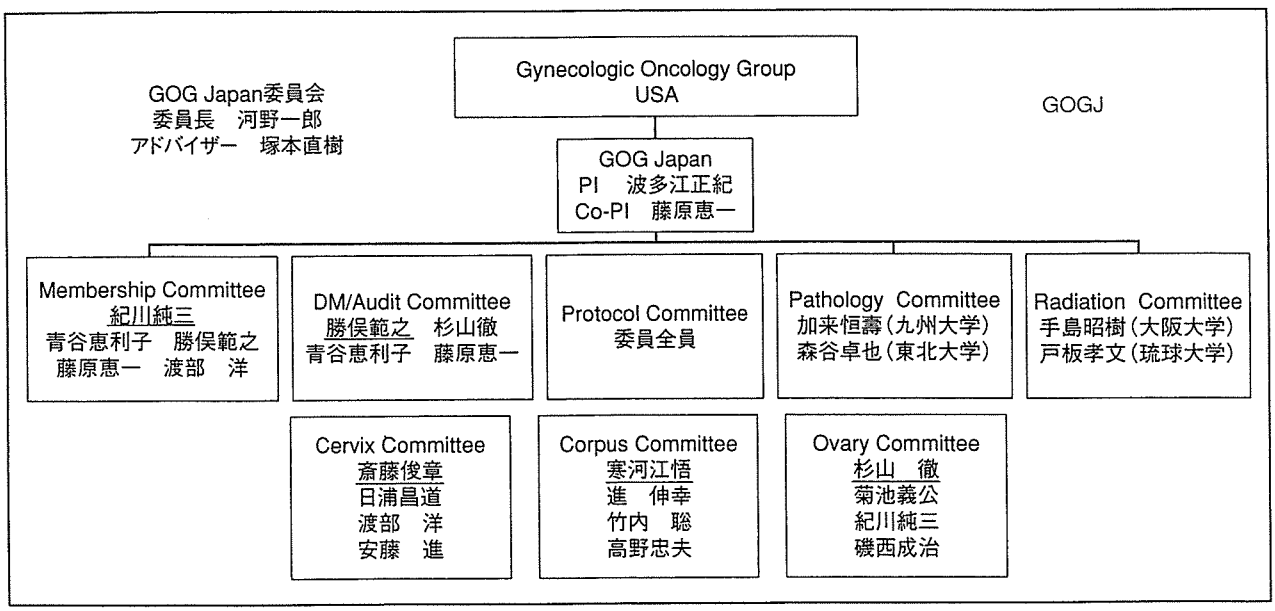

図2　GOG Japan:Structure

1. 臨床研究者グループ

臨床研究の主体をなすところである．医師，Clinical Research Coordinator（CRC），Research Nurseで構成されるが，多くの施設では医師が忙しい診療のなかですべて行っており，かなりの負担となる一方，症例報告書（Case Report Form;CRF）の不備や提出遅延が問題となっている．CRCの教育・導入が少しずつ進んでいるが，資金面より限定された施設に留まる．今後，CRCやResearch Nurseの導入により研究者グ

表1 データセンターの役割

1. 臨床試験の研究デザイン
2. プロトコール作成支援
3. 症例割付
4. 症例登録
5. データマネージメント
6. 統計解析

ループとして，厳格な試験の遂行と正確なデータが迅速に提出できるような体制へと進まねばならない（資金の確保とCRC教育制度）．

2. 支援部門

データマネジャーや生物統計家，コンピュータ技術者などによるデータ管理・統計解析への支援が試験の質の確保において欠かせない（表1）．JCOGでは別項で示されているようにデータマネージメント研究グループが確実に機能しており，JGOGでも北里大学臨床薬理研究所に独立したデータセンター業務を依頼している．データセンターは統計解析に基づいた実施可能性と整合性を重視したプロトコール作成の支援からその試験に関わり，品質管理（Quality Control: QC），品質保証（Quality Assurance: QA）を行い，試験に参加した患者の安全と利益を守り，また，信頼できるデータから正しい結論が得られるように試験の支援を行う．しかし，ここには人件費を含み膨大なお金が必要となり，公的資金に乏しいわが国ではいかにお金を集めるかが問題である．ちなみに，EORTCでは13億の研究費のうち，10億がデータセンターに支払われているし（2001），GOGでも18億中8億が使われている（2001）．

3. 第3者的監視部門

倫理委員会・モニタリング委員会・効果安全性委員会・監査委員会などから構成される．JCOGではauditを行っており，GOG-JapanでもGOGとJGOG合同でのaudit（川崎医大，鹿児島市立病院）を行い，今後，JGOGとしてもJGOG臨床試験へのauditを行っていく予定である．

啓蒙

標準的治療の確立に伴い，治療ガイドラインの作成・実施が望まれる．実際，卵巣がんは欧米でのエビデンスが多く，これに基づいた「卵巣がん治療ガイドライン」が発刊された．しかし，欧米との治療法が異なる部分を有する子宮頸がん・体がんではエビデンスという観点からガイドライン作成は慎重に作業が進められている（婦人科腫瘍学会）．専門医制度や専門医教育が具体化しつつあるが，これらガイドラインを通じて，医師に対して現時点での標準的治療法を示すことが重要である．同時にエビデンスが少ない分野では臨床試験の重要性を認識することに繋がる．一方，臨床試験の足取りを確実なものにするには患者の臨床試験への理解も重要であり，市民公開講座や患者用ガイドラインの作成などの努力が求められる．

おわりに

わが国では患者に標準的治療を提供するという臨床試験を推進・支援・監視する国家機関は存在しないなか，婦人科がんにおける臨床試験への取り組みはその足取りを確実なものとしている．JGOGは国際的にはsystem organizationに先進的なGOGやGCIGと連携することでその方法論を学んでおり，わが国に合ったシステムを作っていく責任がある．国内においてJCOGとJGOGは車の両輪として地方グループと関係を強め，確実な試験の遂行が必要である．しかし，限られた資金のなかでいかに意義ある試験を選び，確実に行っていけるかが今後の課題である．同時に試験に必要な安定した資金の

確保をいかにすべきか，データセンターやCRCの充実など，大きな課題を抱えている．また，臨床試験は標準的治療の確立を目指した研究であることより，得られた結果は確実に国内外で広く公表していかねばならない．これらの積み重ねより，国の臨床試験への理解が深まり，体制が確立されることを期待する．

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婦人科がんを見逃さないために

【婦人科がん早期診断の要点・問題点 4】

卵巣癌

利部 正裕　　杉山 徹

臨床婦人科産科

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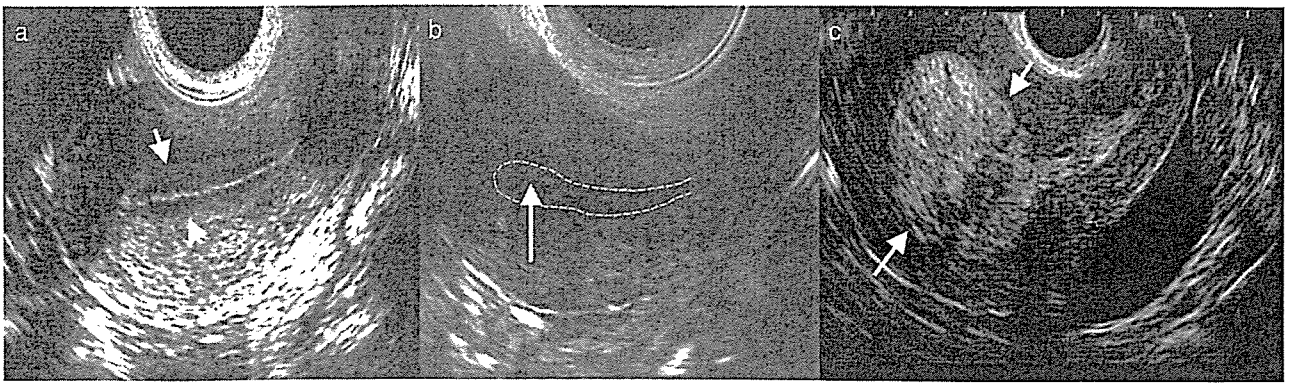

図1　子宮内膜の経腟超音波所見

a：閉経前正常子宮内膜像を示す．子宮内膜は木の葉状を呈し，卵胞期である．
b：閉経後の子宮内膜である．子宮内膜は平滑で萎縮しており，少量の分泌液貯留を認める．
c：子宮体癌の経腟超音波所見を示す．著明な子宮内膜の肥厚と不整な辺縁を呈しており，子宮筋層内への浸潤を認める．また，少量の腹水貯留も認める．pT1cN0M0であった症例である．

においても陰性であった症例，あるいは組織型の決定で判断を迫られる症例に対しての精査の段階では，子宮鏡検査がきわめて有用である．子宮内腔を観察することができ，増殖性病変をピンポイント的に採取できるからである．当院でも組織診において類内膜腺癌G3か漿液性腺癌かの鑑別診断で苦慮する症例を2例経験したが，子宮鏡組織診にて正診を得ている．しかし，子宮鏡試行による悪性細胞の腹腔内への拡散のリスクがあり得ること，さらに，そのような症例の予後に関しての明白なエビデンスがないため[17]，現時点では，細胞診は陽性だが組織診は陰性であるような，いわゆる確定診断が得られない症例に限って行われるべきであろう．

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【婦人科がん早期診断の要点・問題点　4】

卵巣癌

利部 正裕*　　杉山 徹

はじめに

卵巣癌はsilent killerと称されるように初発症状に乏しい．事実，初回診断時に進行癌が約60％以上を占める．5年生存率はⅠ期癌では90％を超えているが，Ⅲ/Ⅳ期は30％前後であり，婦人科癌のなかで卵巣癌は予後が最も不良である．治療法は進歩しているが，早期発見に勝ることはできない．卵巣癌罹患のリスクグループを疫学より知り，症状を振り返り考えてみることで次回からの早期発見へつなげる観点から，また婦人科を訪れた患者に対して卵巣腫瘤を見逃さないコツ，腫瘤が存在すればいかに癌を鑑別するかの観点から，特に最近話題の子宮内膜症からの癌化を含めて考えてみる．さらに，近い将来，血清プロテオミクスでの超早期診断が可能になるであろう．

疫学から危険因子を知る

1．年　齢

年齢が最も重要な危険因子である．米国では発症の平均年齢は59歳で，40～79歳までの発症は15.7から54まで増加する．本邦での人口10万人対の死亡率も55～59歳：11.3から85～90歳：21.5と段階的な上昇を示している[1]．

2．家族性発生

5～10％に家族性発生が報告されている．約70％にBRCA1の変異が関与し，発癌の危険は40％，BRCA2では25％まで高まると報告されている[2]．1親等内に卵巣癌患者がいれば，発症の相対危険率は3.6と報告されている[3]．

3．月経・妊娠歴

妊娠は卵巣癌発生率を10％まで減少させ，未妊婦は危険群に入る．早発初経，晩期閉経も危険を高める[4]．WHOは，ピル内服期間が長いほど卵巣癌の相対危険率が減少すると報告している．

4．ホルモン補充療法

Estrogenを閉経後に10年以上投与すると有意に卵巣癌発生が増加することが報告されている[5]．

5．肥　満

Body mass index (BMI) の増加は危険が高まり，高度なBMIを示した婦人の15％では約2倍の危険性が報告されている[6]．

6．不妊治療

不妊症治療においてclomiphene citrateなどの排卵誘発剤を用い，妊娠が成立しない場合は危険性の増加が指摘されている[7]．Nessら[8]は不妊患者5,207例，コントロール7,705例を11年間追跡して，不妊期間5年以上では1年未満より2.7倍のリスク上昇，borderline serous tumorが2.4倍の発症頻度，内膜症合併では1.7倍の発症頻度と報告している．

症状から

早期症状は非常に乏しく，診断時にⅢ/Ⅳ期癌が過半数を占める．欧米では70～75％がⅢ/Ⅳ期

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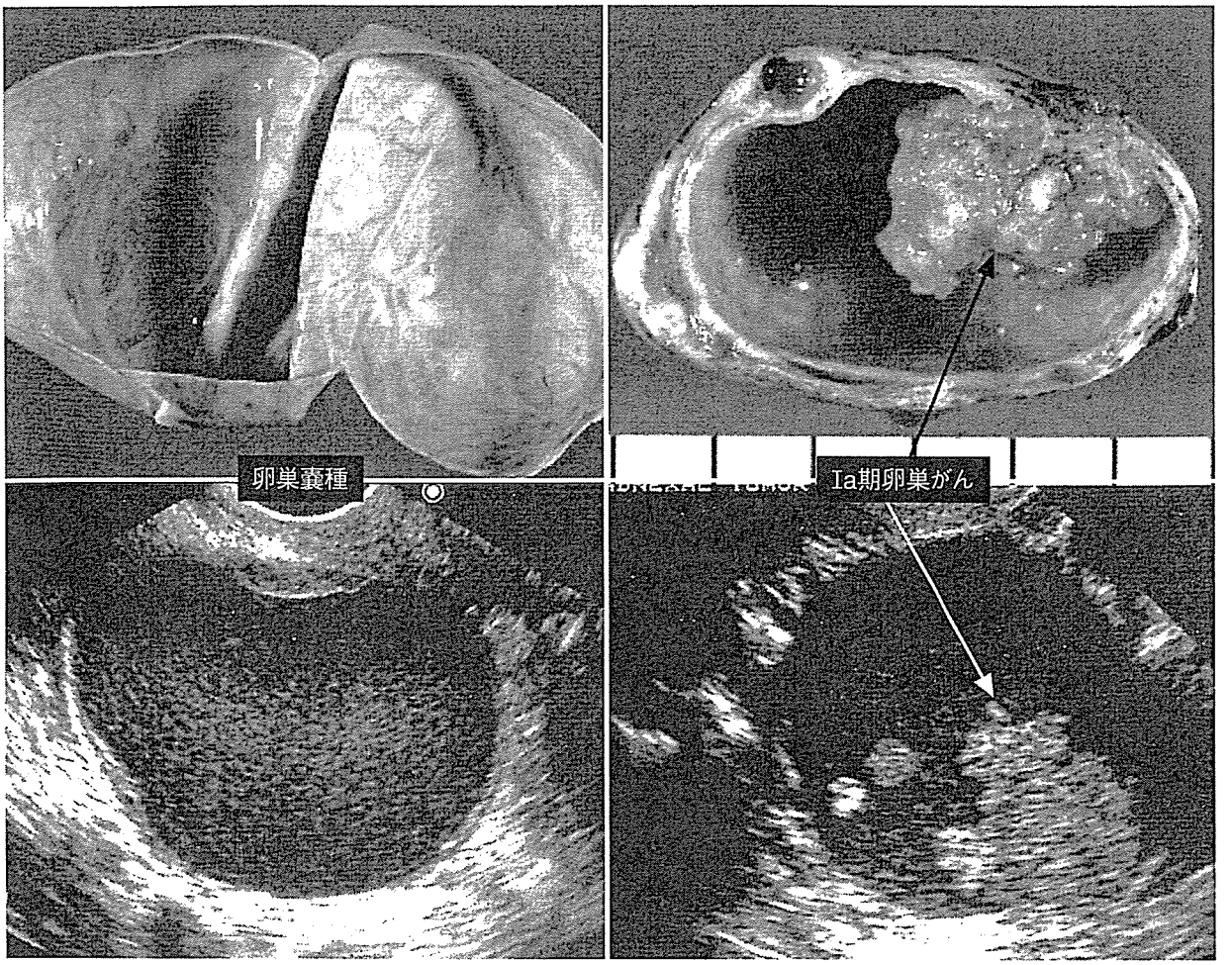

図1　卵巣嚢腫と卵巣癌の肉眼像および超音波所見

癌と報告され，卵巣癌はsilent killerと呼称される．癌はまず腹膜播種にて広く腹腔内へ進展，腫瘤形成に加え，腹水貯留や癌性腹膜炎を伴いやすく，腹囲の増大，膨満感，下腹部痛・下部背部痛，長期間持続する便秘・下痢などが主訴となる．当初，内科などを受診する可能性が高く，他科医師への啓蒙（講演会など）を行い，十分な問診と腹部超音波診を推奨することが早期発見につながる．

産婦人科外来診察時

1．内診と超音波検査

内診では腫瘍の存在がしばしば見逃され，4～6cmの腫瘤の検出率は67％と報告されている[9]．内診に続いて経腟超音波診を行うことが標準的診察手段であり，見逃さないコツでもある．経腟超音波診での形態的なスコアリングが考案されているが，特異性が十分でない．日常臨床での超音波診では，難しく所見を区分することに捉われず，腫瘤が存在したら，大きさを確認後，腫瘤内部構造を観察する．悪性腫瘍であれば，腫瘤壁の肥厚や嚢胞成分に必ず種々の割合で充実成分が混じる．Color doppler imagingがあればこの部分には血流が確認できる．このように，嚢胞成分と充実性成分が混在していないかを厳重にチェックすることがコツである（図1）．悪性が疑われる症例では，詳しい画像診断が必要になる（CT，MRI）．良性腫瘍と考えられたら，手術（腹腔鏡/開腹）が推奨されるが，経過観察の場合は少なくとも3～6か月ごとに厳重な超音波を中心とした画像診断を行うことが必要である．

2．腫瘍マーカー

悪性卵巣腫瘍における主な腫瘍マーカーを表1に示す．非粘液性腫瘍ではCA125が最も特異的であり，卵巣癌の85％が陽性を示すが，Ⅰ期癌

表1　悪性卵巣腫瘍における主な腫瘍マーカー
診断からフォローアップ（治療効果の判定・再発診断）

	組織選択性腫瘍マーカー	一般的腫瘍マーカー
上皮性卵巣腫瘍	CA125　CA19-9 CA72-4　CA546 CA602　SLX　STN	CEA BFP TPA LDH ALP 各種の糖鎖抗原および酵素
胚細胞腫瘍	AFP hCG	
性索間質性腫瘍	estrogen testosterone	

での陽性率は50％にとどまることを知らねばならない．さらにCA125は子宮内膜癌，胆管癌，大腸癌などの悪性腫瘍や子宮内膜症，腹腔内炎症，肝疾患，膵炎などの良性疾患，妊娠初期でも陽性化する．Jacobsら[10]は，閉経後女性においてCA125が30U/m*l*以下の女性と比べ30U/m*l*以上の女性は1年以内に卵巣癌が発見される確率が36倍であり，100U/m*l*以上であれば205倍であると報告している．一方，粘液性腫瘍ではCA125は非特異的であり，CEA，CA19-9，CA724などを参考にする．

検診は有用か

近年，卵巣癌の早期発見を目的として子宮頸がん検診時に経腟超音波を用いて卵巣腫瘍のスクリーニングが行われている．佐藤ら[11]は子宮癌集団検診者延べ20,242人に対して経腟超音波診での卵巣癌検診を行い，卵巣長径が30mm以上あった延べ1,008人に対しての二次検診にて境界悪性・悪性卵巣腫瘍6例を検出している．同時に行ったCA125，CA19-9，AFP，LDHのcombination assay（CAMPAS）での検討も行い，マーカーでの検診では否定的見解を示している．小林[12]は，産婦人科医院・病院を受診した延べ46,394例中287例の卵巣癌を報告している．3～4cmの卵巣腫瘍を見逃さないために経腟超音波診を施行し，そののちに腫瘍マーカー（6種類）でのコンピュータ解析を行うことを推奨している．

岩手県においても1995年より経腟超音波による卵巣癌検診を行っている．再検査の基準としては，閉経前は直径5cm以上の病変を，閉経後は直径3cm以上の病変を腫瘤の性状にかかわらず2次検診とした．その結果，岩手県では検診受診者186,580人中1,095人が要2次検診となり，悪性腫瘍および境界悪性腫瘍が11例（1次検診者の0.006％）であった[13]．しかし，経腟超音波検査だけでのスクリーニングでは不十分であり，CA125と経腟超音波検査との組み合わせが検討されているが，偽陽性率が高い．

いずれにせよ，子宮頸がん対象者に対する卵巣癌検診は，現時点でコストも含めて効率的ではない．

子宮内膜症はがん化する

チョコレート嚢胞の4～5％に卵巣癌が合併し，卵巣癌の16～17％にチョコレート嚢胞が合併する．チョコレート嚢胞（全年齢）のがん化率は0.7％，年齢や腫瘍径に相関してがん化率が上昇することが報告された[14]．また，Gorpら[15]は，子宮内膜症の2.5％に癌化の可能性があると述べている．子宮内膜症取扱い規約（2004版）[16]には，「endometrial cyst合併卵巣癌に対するガイドライン（卵巣チョコレート嚢胞の悪性化）」という項目が記載された．チョコレート嚢胞は画像（超音波，MRI/CT），腫瘍マーカー（CA125，CA19-9）での3～6か月ごとのフォローアップが必要である．また，年齢（＞40歳）・腫瘍径（＞10cm）によりがん化のリスクは高まるので，20～30歳代でも10cmを超える場合や腫瘍径にかかわらず40歳（特に50歳）を超えた場合は，がん化前の摘

出術（開腹・腹腔鏡）を検討する．

血清プロテオミクス

早期卵巣癌を発見するための診断用血清バイオマーカーの探索が重要な課題であり，われわれはKKKS臨床プロテオミクス研究会（NPO）を組織して世界に先駆け子宮体癌での第1段階の解析を行った．卵巣癌に関しても報告はきわめて限られており[17]，現在，試験の準備中である．

おわりに

早期癌早期診断のポイントは以下の通りである．（1）卵巣癌の発症リスクを知る．（2）内科医などへの啓蒙（腹部超音波）．（3）婦人科受診時の内診・経腟超音波の重要性．（4）適切な検診システムの構築．（5）子宮内膜症への注意．そして，プロテオミクス研究の推進が必要である．

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【婦人科がん早期診断の要点・問題点　5】

卵管癌

三宅 貴仁*　　榎本 隆之

はじめに

卵管癌は婦人科腫瘍のなかでも非常に稀な疾患であり，その頻度は全婦人科腫瘍の約0.3％といわれている．組織学的な形態，特徴から卵管癌は卵巣癌と非常に類似しており，その診断，治療は卵巣癌と同様に行われる．大半は上皮由来であるが，肉腫を認めたという報告もある．

症　状

卵管癌は50歳代から60歳代にかけてみられることが多く，平均年齢は55歳から60歳である．典型的な三徴は水様帯下，下腹部痛，骨盤内腫瘤とされているが，これらすべての症状が認められる症例は15％以下である[1]．症状がなく，他疾患での子宮摘出，付属器摘出の際に偶然みつかることも多い．

最もよく認められる症状は性器出血，下腹部痛，骨盤痛であり，50％以上の症例で認められる．下腹部痛，骨盤痛は卵管壁の伸展に伴うもので，出血を伴う仙痛として自覚されることが多い．症状が長期間持続することも特徴的であり，半数以上の症例で症状が2か月以上持続していたという報告もある[2]．しかしながら，このような症状は非特異的であるため，症状出現から診断に至るまで4か月以上経過している症例が半数以上との報告もある[3]．

卵管癌の早期発見は非常に困難であるが，閉経後女性で原因不明の帯下増量を認め持続する場合，不正出血が持続する場合には卵管癌の存在も念頭に置いて精査を進める必要がある．

診　断

術前に卵管癌の診断がつくことは非常に稀である．約60％の症例に骨盤内の腫瘤を認め，病変が進行している場合には腹水も認められる．このために卵巣癌との鑑別が問題となるが，超音波画像，MRI，腫瘍マーカーなどで両者を鑑別することは困難なことが多い．

近年，卵管癌の診断にMRIやCTを使用した報告も認められる．術前診断が可能であった卵管癌症例のMRI画像を図1に示す．川上ら[4]は帯下増量や不正出血を認める症例で，付属器領域に小さく充実性で分葉状の腫瘤を認め，子宮内に液体貯留を認める場合には卵管癌も鑑別診断に挙げておくべきであると報告している．また，子宮筋腫，卵巣腫瘍などとの鑑別にはCTよりもMRIが有用であるとも報告している．

卵巣癌における超音波診断についてはあまり報告がないが，複雑な形態をした大部分が嚢腫状で，一部に壁在結節を認める付属器腫瘤，明らかに子宮から離れた部位に存在するソーセージ様腫瘤として描出されることが多いという報告がある[5,6]．当科で経験した卵管癌症例の超音波画像を図2に示す．血流ドプラを用いることで，腫瘍内の血管

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REVIEW ARTICLE

Disparities in Gastric Cancer Chemotherapy Between the East and West

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ABSTRACT

There are still remarkable disparities in the treatment of gastric cancer between the East and West. Treatment outcomes for this disease have improved in Japan due to early detection and surgical resection with systematic node dissections, such as D2, whereas gastric cancer remains a virulent disease in Western countries. Differences in the types of surgery and their outcomes affect how adjuvant trials are conducted and interpreted. Recent Western randomized trials demonstrated the significant survival benefit of adjuvant chemoradiotherapy or intensive combination chemotherapy. However, baseline surgical quality and outcomes were quite different from those in Japan, and Japanese surgical/medical oncologists have not accepted the Western results. Several disparities are also evident in the results of chemotherapy trials for advanced gastric cancer. Although similar results were obtained with randomized studies using older regimens, the interpretation of the results differed between Japan and other countries. A combination of cisplatin and fluorouracil was used as the reference arm in ongoing randomized trials in most countries, whereas single-agent fluorouracil or *S*-1 alone was used in Japanese trials. Two triplet regimens have already demonstrated significant prolongation of survival in Western studies. However, these benefits seem to be marginal and these regimens may be replaced by newer regimens, which will soon be available in Europe and Asia, where a total of 2,600 patients have been accrued. Although these disparities between regions must be overcome, it is time for both Eastern and Western investigators to pursue further benefits by incorporating new agents into treatment regimens.

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INTRODUCTION

According to global estimates of cancer incidence in the year 2002, gastric cancer is the second most frequent cancer-related cause of death after lung cancer. The incidence of gastric cancer was estimated to be 934,000 cases, with 56% of the new cases occurring in East Asia; 41% in China, and 11% in Japan.[1] Although the incidence of gastric cancer has decreased in recent years and its mortality rate in Japan is now lower than that of lung cancer, it still has the highest incidence.

Significant differences have been observed among the 5-year survival rates in Japan and other countries. Based on data from population-based cancer registries, the survival rate is higher in Japan (40% to 60%)[2,3] than in other countries (approximately 20%).[4,5] In Japan, a nationwide mass screening system has been developed that has resulted in the diagnosis of a large proportion of gastric cancers at an early stage: 53% of Japanese gastric cancers were localized when diagnosed, compared with only 27% of those in the United States population. Today in Japan, approximately 50% of patients with stage IA gastric cancer are treated with endoscopic mucosal resections, as has been documented precisely in a recent review in the *Journal of Clinical Oncology*.[6]

Another cause of the higher survival rate in Japan is thought to be the use of radical surgery. Gastrectomy with the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches), known as D2 dissection, is the standard surgical technique used in Japan, whereas D1 dissection is used in Western countries. Two European randomized trials that compared D1 and D2 gastrectomy failed to demonstrate any survival benefit of D2 over D1.[7,8] However, this failure was predominantly caused by the high mortality rate in the D2 group, which exceeded 10%, a rate that most Japanese surgeons and medical oncologists find unacceptable. The Japanese nationwide registry reported an operative mortality rate of less than 2%,[9] and the recent report of a large randomized trial comparing D2 dissection with D2 plus para-aortic nodal dissection, by the Japan Clinical Oncology Group (JCOG 9501), showed a hospital mortality rate of only 0.8%.[10] One of the major criticisms of Japanese surgery is that most of the data from Japan have been based on retrospective or small studies. JCOG 9501 trial circumvents these criticisms. Japanese surgeons believe that D2 gastrectomy imposes a steep learning curve and may be associated with higher than expected operative morbidity and mortality. Furthermore, major US cancer centers with extensive experience have also achieved

low mortality rates of 1.7% to 3.6%.[11,12] The protracted debate regarding the survival benefit of lymphadenectomy persists between the West and Japan, and also Korea, where D2 gastrectomy has been well accepted with survival and mortality rates similar to those of Japan.[13,14] Although this issue should be clarified in future clinical trials, these marked differences in survival and morbidity and mortality rates after surgery have also caused the planning and interpretations of adjuvant and neoadjuvant trials to differ between Western countries and East Asia.

In contrast to the marked differences in the surgery used to treat gastric cancer, there seem to be fewer differences in the results of the chemotherapy used to treat metastatic gastric cancer. However, a few agents display ethnic differences, and there are some cultural and regulatory differences between the West and Japan in interpreting the results of clinical trials. The number of international studies has recently increased annually, and these regional differences are one of the major obstacles to be overcome in these studies. This review focuses on the disparities in the treatment of gastric cancer between the East and West, particularly in adjuvant and neoadjuvant and primary chemotherapy trials.

ADJUVANT AND NEOADJUVANT TRIALS

The survival benefits of adjuvant chemotherapy have long been argued. In 1993, Hermans et al[15] reported the results of a meta-analysis of 11 randomized trials that compared surgery alone with postoperative adjuvant chemotherapy. The analysis produced no definite evidence of significant survival benefit for adjuvant chemotherapy, but was followed by contrary results in an updated analysis.[16] Two recent reports of meta-analyses showed a significant survival benefit for adjuvant chemotherapy. However, the methodologies of these meta-analyses varied and the benefit of adjuvant chemotherapy was so small that there was insufficient evidence to recommend adjuvant chemotherapy as the standard treatment.

Historically, earlier adjuvant studies in Japan were carried out with mitomycin C (MMC) and/or oral fluorouracils. These studies produced conflicting results in terms of the survival benefit of adjuvant chemotherapy.[17-20] Possibly because of the immature infrastructure available for clinical trials, and particularly the quality control of the studies, the 5-year survival rate of the surgery-only group in each study varied, which might explain the conflicting results. Against this background, the JCOG undertook a large multi-institutional randomized study in the late 1980s that compared surgery alone with surgery plus adjuvant chemotherapy consisting of intravenous infusion of MMC + fluorouracil (FU) followed by oral uracil and tegafur (UFT; JCOG 8801) for patients with macroscopically defined T1 or T2 tumors, who had received curative resections.[21] With a median follow-up of 72 months, no significant differences in survival between the two groups were observed; the 5-year survival rates of the control and treatment groups were 82.9% and 85.8%, respectively. In this study, the 5-year survival rate of patients with T1 cancer in the control group was 94.9%, which led Japanese investigators to exclude these patients from the following adjuvant trials, and from programs of adjuvant chemotherapy in daily practice. The subsequent adjuvant randomized trials undertaken by the JCOG were divided into two studies: one targeted macroscopically serosa-negative cancers excluding T1N0 cancers (JCOG 9206-1), and the other targeted macroscopically serosa-positive gastric cancers (JCOG 9206-2). The former study (JCOG 9206-1) compared surgery alone with surgery plus intravenous MMC, FU, and cytarabine, followed by oral FU, and the results have already been published (Table 1).[22] Although there was a trend of increased survival in the adjuvant chemotherapy group, this study failed to demonstrate a significant difference in relapse-free or overall survival between the two arms. The 5-year relapse-free survival rates of the chemotherapy and control groups were 88.8% and 83.7%, respectively ($P = .14$), and their 5-year overall survival rates were 91.2% and 86.1%, respectively ($P = .13$). More recently, the positive results of another randomized trial by the National Surgical Adjuvant Study for

Table 1. Results of Recent Randomized Trials of Adjuvant Chemotherapy/Chemoradiotherapy Versus Surgery Alone

Study	Stage	Treatment	No. of Patients	5-Year RFS (%)	5-Year Survival (%)	*P*
Japanese trials						
Nashimoto et al[22] JCOG 9206-1	T1-2 excluding T1N0	FU + MMC + Ara C	128	88.8	91.2	NS
		Surgery alone (D2)	124	83.7	86.1	
Kinoshita et al[23] NSASGC	T2N1-2	UFT	93	84.5*	86.3*	.0176
		Surgery alone (D2)	95	68.1	73.6	
Miyashiro et al[24] JCOG 9206-2	T3-4	FU + CDDP/UFT	135	59.0	62.7	NS
		Surgery alone (D2)	133	57.1	61.6	
Western trials						
Bajetta et al[27] ITMO	N+ or T3-4	Etoposide + ADM + CDDP	137	49	52	NS
		Surgery alone (D2)	137	44	48	
Cunningham et al[28] MAGIC	Including GEJ/lower E	Epirubicin + FU + CDDP	250		36	.009
		Surgery alone	253		23	
MacDonald et al[30] INT 016	T1-4	FU/LV + RT (45 Gy)	281	48†	50†	.005
		Surgery alone (D0 > 1)	275	31	41	

Abbreviations: RFS, relapse-free survival; JCOG, Japan Clinical Oncology Group; FU, fluorouracil; MMC, mitomycin; Ara C, cytarabine; NS, not significant; NSASGC, National Surgical Adjuvant Study for Gastric Cancer; UFT, uracil and tegafur; CDDP, cisplatin; ITMO, the Italian Trials in Oncology Group; ADM, doxorubicin; MAGIC, MRC Adjuvant Gastic Cancer Infusional Chemotherapy; GEJ, gastroesophageal junction; E, esophagus; INT, US Intergroup study; LV, leucovorin; RT, radiation therapy

*At 4 years.

†At 3 years.

Gastric Cancer (NSASGC) have been reported in abstract form.[23] Patients with histologic T2 cancers (N1-2 in the Japanese staging system), who had been treated with curative gastrectomy, were eligible for this study and were randomly assigned to either surgery only or adjuvant chemotherapy comprising UFT alone for 16 months. This study was designed to accrue 244 patients, but closed with a total of 190 patients because of slow recruitment. In an interim planning analysis, the chemotherapy group demonstrated a significant survival benefit over the surgery alone group, in both relapse-free and overall survival. Four-year survival rates in the chemotherapy and control groups were 86.3% and 73.6%, respectively ($P = .0176$), and the relapse-free survival rates were 84.5% and 68.1%, respectively ($P = .0040$). Contrary to the results of the NSASGC study, the JCOG 9206-2 study, which targeted serosa-positive (T3 or T4) cancers, recently demonstrated no advantage for adjuvant chemotherapy.[24] This study compared surgery alone with surgery plus adjuvant chemotherapy consisting of intraperitoneally administered cisplatin (CDDP) at the time of surgery, one course of intravenous CDDP and FU, followed by oral administration of UFT for 12 months. A total of 268 patients were accrued; the 5-year overall survival rates in the chemotherapy and control groups were 62.7% and 61.6%, respectively ($P = .48$), and the relapse-free survival rates were 59.0% and 57.1%, respectively ($P = .5$).

Several criticisms can be made of these Japanese studies. These studies had limited statistical power to detect survival differences due to small sample sizes. For instance, in the JCOG 9206-1 study, the expected difference in 5-year survival between the two arms was 15%, which seems unrealistic when the power of chemotherapy is considered. Subdividing the stages in each study also contributed to the small sample sizes. In addition, the survival results of the control groups were inconsistent in each study. In JCOG 9206-1, the expected 5-year survival rate of the control group was estimated to be 70% based on the results of a previous study, whereas the actual 5-year survival rate was 83.7%. However, this increase seems to have been caused by an improvement in the quality control of the studies. As described in the report of another JCOG study, only selected surgeons with extensive experience could participate in the study.[10] This selection criterion might have improved the survival of the control group. A similar phenomenon was observed in adjuvant studies of cancers at other sites, such as colon cancer. The chemotherapy regimens and the doses used in each study varied and may have been inadequate. Most of the regimens used in these adjuvant trials in Japan were not based on sufficient evidence of their efficacy in treating metastatic disease. Moreover, the doses used in the studies (except the NSASGC study) were lower than usual doses. With respect to oral fluorouracils, oral FU (134 mg/m^2 per day) was administered in the JCOG 9206-1 study and oral UFT (267 mg/m^2 per day) in the JCOG 9206-2 study, which are considered to be insufficient doses for efficacy. The differences in the doses of UFT between the NSASGC and JCOG studies may have caused the contradictory results. The small sample size of the NSASGC study means that no definitive advantage of adjuvant chemotherapy following standard gastrectomy with D2 dissection has been demonstrated yet in Japan. However, these studies have confirmed the survival benefit of surgery, with a 5-year survival rate higher than 60%, even in patients with T3 or T4 cancers. Recently, a large-scale randomized trial of 1,000 patients that compared surgery alone with adjuvant chemotherapy using S-1 was undertaken in Japan and accrual has already been completed. This study targets a wide population with stage II and III cancers and uses standard doses of S-1. The results of this study will allow definitive conclusions to be drawn and should circumvent these criticisms.

In contrast, the usefulness of intensive adjuvant chemotherapies has been challenged in Western countries. Earlier Western randomized trials investigated the use of FU, doxorubicin, and MMC as adjuvant therapies. They failed to demonstrate a significant survival advantage of adjuvant chemotherapies over surgery alone.[25,26] Another trial, using an intensive combination regimen comprising etoposide, doxorubicin, and CDDP, was reported by an Italian group.[27] A total of 274 patients were randomly assigned to surgery alone or surgery plus two courses of etoposide, doxorubicin, and CDDP followed by FU + leucovorin. It is of note that this study used D2 dissection as the surgical procedure and the pathologic documentation of second tier nodes, consistent with Japanese guidelines. Although there were no significant differences in survival (5-year survival rates of the chemotherapy and control groups were 52% and 48%, respectively), Bajetta et al concluded that D2 surgery might have a favorable impact on survival because the 5-year survival rate observed in the control group was remarkably higher than expected (30%) when the protocol was designed. More recently, the Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) study in the United Kingdom reported the survival benefit of perioperative chemotherapy.[28] This study adopted a three-drug combination regimen consisting of epirubicin (50 mg/m^2) and CDDP (60 mg/m^2) every 3 weeks, and FU (200 mg/m^2 per day) for 3 weeks (ECF regimen), based on the positive results of a randomized trial for the treatment of metastatic gastric cancer.[29] Patients with operable adenocarcinoma of the stomach, gastroesophageal junction, or lower esophagus were randomized into either surgery alone or perioperative treatments with chemotherapy comprising three preoperative and three postoperative courses of ECF. With a median follow-up of longer than 3 years, the perioperative chemotherapy group showed significantly better survival and progression-free survival than the control group. The 5-year survival rates of the chemotherapy and control groups were 36% and 23%, respectively ($P = .009$).

Another approach to the improvement of survival in the United States, where locoregional recurrence rates are high, is with postoperative chemoradiotherapy, which has also been challenged. The U.S. Intergroup study INT0 116 was a large-scale randomized trial comparing surgery alone with surgery plus chemoradiotherapy consisting of FU + leucovorin and 45 Gy of radiation. The results of this study were published in 2001 and updated in 2004.[30,31] This study clearly demonstrated significantly better survival and locoregional control in the chemoradiotherapy group than in the control group. Median disease-free survival in the chemoradiotherapy and control groups was 30 and 19 months, respectively ($P < .001$) and overall survival was 35 and 26 months, respectively ($P = .006$).

Although the two reports from the West described above have demonstrated the positive impact of adjuvant therapies, several issues are still open to criticism, as in the Japanese studies. The biggest issue is the quality control of surgery in these studies, particularly in the INT0 116 study, in which only 10% of patients underwent D2 dissection and 54% of patients underwent D0 (not D1) dissection. Furthermore, retrospective analysis of this study demonstrated that surgical undertreatment reduced survival.[32] The 5-year survival rate was around 40%, even in the chemoradiotherapy group, which seems remarkably lower than that for D2 surgery alone in both the Japanese and the Italian studies.[27,33] In Japan, where D2 is the standard surgical procedure and locoregional recurrence is rare, the results of this trial would be interpreted as demonstrating that D0/1 plus chemoradiotherapy is better than D0/1

alone but probably no better than D2 alone. Due to the low incidence of locoregional recurrence in Japan, the role of radiotherapy in gastric cancer should be very limited. A similar criticism might be leveled at the MAGIC trial, although this study has only been reported in abstract form and the types of surgery evaluated were not specified. However, the chemotherapy group showed an even worse 5-year survival rate after D2 surgery alone than that reported in the Italian study. This study also included lower esophageal cancers, which confuses the interpretation of the trial. The staging system and types of surgery used to treat esophageal cancer are quite different from those used for gastric cancer in Japan, although adenocarcinoma of the lower esophagus is still rare. Whether the biologic behavior of this tumor is different from that of squamous cell carcinoma is unknown to Japanese investigators.

There are great disparities in the interpretation of adjuvant trials between the West and Japan, mostly caused by different baseline results of surgery. These differences appear to be caused not only by differences in surgical techniques but also by differences in diagnostic techniques. Japanese gastroenterologists and pathologists also have advanced techniques for the accurate estimation of the extension margin or staging. Although Western randomized trials comparing D1 with D2 have not demonstrated any superiority of D2, and stage migration might affect survival after D2, it seems unlikely that Japanese investigators will accept the results of Western trials. In this regard, the interpretation of adjuvant trials will differ, based on baseline types of surgery. Chemoradiotherapy could compensate for inadequate surgery, such as D0 dissection, and ECF could provide a survival advantage after D1 surgery, whereas the benefit of adjuvant chemotherapy after D2 surgery has yet to be confirmed. To identify a small increment in the cure rate caused by adjuvant chemotherapy, larger sample sizes are required in randomized studies, as observed in colorectal studies, for which international studies are now becoming common. Japanese investigators should also conduct international studies with other countries in which D2 is the standard surgical practice, such as Korea. Newer regimens, with more evidence of success with metastatic disease, as described in the following paragraph, should be included in future trials.

CHEMOTHERAPY TRIALS FOR ADVANCED DISEASE

Unresectable advanced or recurrent gastric cancers still have poor prognoses. Randomized trials have demonstrated that FU-based regimens provide superior survival and quality of life in patients with advanced gastric cancer when compared with the results of the best supportive care.[34-36] However, this survival advantage appears to be marginal and no standard regimens have yet been established worldwide.

DISPARITIES IN INTERPRETING THE RESULTS OF PREVIOUS RANDOMIZED CONTROLLED TRIALS

During the past two decades, various randomized trials have been performed to evaluate treatments for metastatic gastric cancer. Three randomized trials that included FU alone as the reference arm and compared it with older FU-based combination regimens have been reported in the United States, Korea, and Japan (Table 2).[37-39] All three trials had similar results. No combination regimen demonstrated survival prolongation compared with that of FU alone, whereas the response rates and progression-free survival in the CDDP + FU (CF) arm were better than those of single-agent FU in the Korean (median survival times [MSTs] of 8.5 and 6.9 months, respectively) and Japanese studies (MSTs of 7.3 and 7.1 months, respectively). However, the interpretation of these results, particularly when determining the reference arms of subsequent studies, differed between regions. Most countries other than Japan considered CF as a following reference arm, without definite evidence of superiority over single-agent FU, because this monotherapy had only limited activity, with a response rate of around 10% and median progression-free survival of approximately 2 months. It would be advantageous for CF that a higher response rate could improve the symptoms of the patients. In Japan, single-agent FU was selected as the subsequent reference arm, because no differences in overall survival were observed and the primary end point of the study was overall survival. The CF regimen provided significantly longer progression-free survival, but no better overall

Table 2. Results of Randomized Trials Using Older Regimens

Study	Treatment	No. of Patients	Response Rate (%)	Median Survival (months)	*P*
Korea[38]	FU	94	26	6.9	NS
	FU + ADM + MMC	98	25	6.6	
	FU + CDDP	103	51	8.5	
JCOG 9205[39]	FU	106	11	7.1	NS
	FU + CDDP	104	34	7.3	
	UFT + MMC	70	9	6.0	
EORTC[40]	FU + ADM + MMC	103	7	6.7	004
	FU + ADM + MTX	105	33	9.6	
UK[42]	FU + ADM + MTX	130	21	5.7	.0009
	Epirubicin + CDDP + FU	126	45	8.9	
EORTC[41]	FU + CDDP	134	20	7.2	NS
	Etoposide + LV/FU	132	9	7.2	
	FU + ADM + MTX	133	12	6.7	

Abbreviations: FU, fluorouracil; NS, not significant; ADM, doxorubicin; MMC, mitomycin; CDDP, cisplatin; JCOG, Japan Clinical Oncology Group; UFT, uracil and tegafur; EORTC, European Organisation for Research and Treatment of Cancer; MTX, methotrexate; UK, United Kingdom; LV, leucovorin.

survival, and a significantly higher incidence of toxicity compared with that of the control arm, FU alone.

In Europe, triplet regimens have been commonly used. A combination of FU, doxorubicin, and high-dose methotrexate (FAMTX) used to be a standard regimen, based on European Organisation for Research and Treatment of Cancer trials.[40] However, this regimen failed to demonstrate any superiority to other combination regimens, such as CF or etoposide + FU + leucovorin, in the following European Organisation for Research and Treatment of Cancer randomized study.[41] Another randomized study in the United Kingdom revealed the superiority of a combination of epirubicin, cisplatin, and FU (ECF) over FAMTX in terms of survival,[29] whereas there was some debate about the methodologies of the clinical trials and the inconsistent results obtained with FAMTX during the European trials.[42,43] The survival results in these studies were limited, with an MST ranging from 6 to 8 months, and no improvement with the addition of epirubicin to CF has yet been confirmed. ECF still has limited acceptance as a standard treatment for metastatic gastric cancer. This regimen is used only in the United Kingdom and parts of Europe.

Although there are significant differences in the historical backgrounds and interpretations of results between regions, the results for CF in Europe, North America, Korea, and Japan are very similar, as shown in Table 3.[38,39,41,44] Median progression-free survival (PFS; given as the time to progression in two studies) ranged from 3.7 to 5.0 months, with MSTs ranging from 7.2 to 8.5 months. Contrary to the disparities in the adjuvant trials, there were no significant differences in the biologic responses to chemotherapy between regions.

RESULTS OF RECENT STUDIES WITH NEW REGIMENS

During the past decade, a new generation of agents has been developed, including irinotecan, S-1, capecitabine, docetaxel, paclitaxel, and oxaliplatin, which have shown promising activities in single-agent studies[45-50] and when investigated in combination with other agents. Numerous combinations have been reported as phase II settings, and promising regimens that have been included in recent ongoing randomized trials are summarized in Table 4.[51-55] These regimens have achieved better median times to progression (approximately 6 months) and MSTs (approximately 10 months) compared with those of older regimens, although definite conclusions should not be drawn until the results of randomized trials are available.

Recently reported and ongoing large-scale randomized trials are listed in Table 5. Most of the trials outside Japan used CF as the control arm and one trial used ECF as the control arm, whereas the Japanese studies used single-agent FU or S-1 as the control arm. These disparities are considered to result from the different interpretations of the results of previous randomized studies, as described in the preceding section.

Table 3. Treatment Results of Cisplatin/Fluorouracil for Advanced Disease in Randomized Trials

Trial	No. of Patients	Response Rate (%)	Median PFS (months)	Median Survival (months)
Japan[39]	105	34	3.9	7.3
Korea[38]	103	51	5.0	8.5
EU[41]	134	5.0*	4.1	7.2
US/EU[44]	112	23	3.7*	8.5

Abbreviations: PFS, progression-free survival; EU, Europe; US, United States.
*Estimated as median time to progression.

Table 4. Treatment Results of Newer Generation Included in Ongoing Randomized Trials

Regimen	No. of Patients	Response Rate (%)	Median TTP (months)	MST (months)
Irinotecan + CDDP[51]	38	58	5.6	9.0
Irinotecan + FU/LV[52]	59	42	6.5	10.7
S-1 + CDDP[53]	25	76	6.0	12.5
S-1 + Irinotecan[54]	24	50	6.0	NS
Capecitabine + CDDP[54]	42	55	6.3	10.1
Docetaxel + CDDP[55]	63	28	5.0	10.5
Docetaxel + CDDP + FU[55]	61	43	5.9	9.6

Abbreviations: TTP, time to progression; MST, median survival time; CDDP, cisplatin; FU, fluorouracil; LV, leucovorin; NS, not stated.

Recently, a large-scale international randomized controlled trial (V325) comparing docetaxel + CDDP + FU (DCF) with CF has been reported in abstract form (Table 6).[44] The initial phase II randomized part of this study, comparing docetaxel + CDDP with DCF, revealed a better response rate and time to progression with DCF.[55] The DCF regimen was then chosen as the experimental arm for the phase III stage. The doses and schedules for the DCF arm were docetaxel (75 mg/m^2) on day 1, CDDP (75 mg/m^2) on day 1, and FU (750 mg/m^2 per day) as a continuous infusion on days 1 through 5, repeated every 3 weeks. Those for the CF arm were CDDP (100 mg/m^2) on day 1 and FU (1,000 mg/m^2 per day) as a continuous infusion on days 1 through 5, given every 4 weeks. The primary end point was time to progression, whereas overall survival, duration of response, safety, and quality of life were secondary end points. A total of 457 chemotherapy-naive patients were registered. The final results of this study clearly demonstrated the superiority of DCF to CF: time to progression was longer for DCF, with a median of 5.6 months, than for CF (3.7 months; $P = .0004$). Overall survival was also longer for patients receiving DCF, with an MST of 9.2 months, than for those receiving CF (8.6 months; $P = .0201$). Neutropenic fever, infections, diarrhea, and mucositis were more frequent in the DCF group than in the CF group, whereas a better quality of life, including global health status, was maintained for a longer period with the DCF regimen. An open question remains in the interpretation of these results. The MST of the DCF arm was less than 10 months and survival improvement was less than 1 month as compared with CF, despite substantial toxicity. These facts cause many investigators to hesitate in accepting this regimen as the standard treatment. However, this study clearly demonstrated the efficacy of docetaxel, and this agent should constitute part of the frontline therapies for advanced gastric cancer.

Another international randomized phase II/III study (V306) has recently been reported. This study initially compared irinotecan + CDDP with irinotecan + infusional FU + leucovorin in the phase II part of the study, to determine the experimental arm of the phase III trial with CF.[52] In this study, irinotecan (200 mg/m^2) and CDDP (60 mg/m^2) were administered every 3 weeks, and compared with irinotecan (80 mg/m^2), leucovorin (LV; 500 mg/m^2), and FU (2,000 mg/m^2) administered as one 24-hour infusion per week for 6 weeks, followed

by a 1-week respite. The overall response rates for irinotecan + CDDP and irinotecan + FU + LV were 32% and 42%, respectively, and MSTs were 6.9 and 10.7 months, respectively. Toxicity results also revealed more favorable profiles for irinotecan + FU + LV than for irinotecan + CDDP. Therefore, the former regimen was chosen as the experimental arm for the phase III part of the study for comparison with the control arm of CF. In the full analysis population of 333 patients, the irinotecan-based regimen demonstrated a trend toward a longer time-to-progression and greater overall survival. However, these differences were not statistically significant (hazard ratios: 1.23 and 1.08, respectively).[56] Median times to progression for irinotecan + FU + LV and CF were 5.0 and 4.2 months, respectively, and the MSTs of both arms were less than 10 months. More patients withdrew from the study because of drug-related adverse events with CF than with irinotecan + FU + LV (21.5% and 10.0%, respectively; $P = .004$). Based on the results of the V306 study, irinotecan + FU + LV can be considered a reasonable alternative first-line treatment option without CDDP, but it provides no definite efficacy advantage over CF.

In the United Kingdom, where ECF is the standard treatment, the REAL-2 study is now underway. This study uses a 2 × 2 design to evaluate several modifications of ECF: substitution of capecitabine for FU and substitution of oxaliplatin for CDDP. Patients were randomly assigned to one of the four regimens: ECF, epirubicin + oxaliplatin + FU, epirubicin + CDDP + capecitabine, or epirubicin + oxaliplatin + capecitabine. The interim analysis with a total of 204 patients showed response rates of 31%, 39%, 35%, and 48% for ECF, epirubicin + oxaliplatin + FU, epirubicin + CDDP + capecitabine, and epirubicin + oxaliplatin + capecitabine, respectively.[57] The accrual of 1,000 patients has already been completed and the final results will appear in 2006. In Korea, where many combination phase II studies that include capecitabine have been developed, a randomized trial comparing capecitabine + CDDP with CF is now underway in collaboration with other Asian countries. This study has already achieved the final accrual of 300 patients and the results will be presented in 2006.

In contrast, three randomized trials using an *S*-1-based regimen are now being investigated in Japan. Following the results of the JCOG 9205 trial, the JCOG initiated three arm randomizations (JCOG 9912) comparing FU alone with a combination of irinotecan + CDDP and with *S*-1 alone, based on the promising results of phase II studies in Japan.[48,49,58] This study requires a sample size of 700 and its accrual has recently been completed. The other two studies use *S*-1 monotherapy as the control arm, for comparison with *S*-1 + CDDP[59] (Taiho trial) or *S*-1 + irinotecan[59] (Yakult-Daiichi trial), for which the accruals have also been completed, with 300 patients each. The primary end point of all three trials is overall survival and final data on the total 1,300 patients will be available early in 2007.

There are several disparities between the Eastern and Western trials that have evaluated treatments for advanced cancer, as seen in the adjuvant trials. CF or partial ECF were used as the control arms in the studies outside Japan, whereas monotherapies such as FU or *S*-1 alone were used in the Japanese studies. These differences arose from different interpretations of previous trials, as described above. Usually, more than 50% of patients receive second-line or additional chemotherapy after the failure of a first-line therapy. In this regard, the monotherapy arm could represent a sequential combination therapy and, therefore, monotherapy versus combination therapy can be regarded as sequential combination therapy versus simultaneous combination therapy. These debates should be resolved by the ongoing Japanese studies, and the impact of second- or higher line therapies with new generation agents can be estimated by comparing the results for the FU monotherapy arms between the JCOG 9205 and 9912 trials.

The primary end points also differed among the studies. The V325, V306, and Korean studies adopted time to progression as the primary end point, whereas the end points of the REAL-2 and Japanese studies were overall survival. There exists a debate over whether time to progression can be replaced by overall survival as the primary end point in randomized studies of gastric cancer. It seems difficult to achieve a prolongation of overall survival using only first-line treatments because of the influence of subsequent treatments, particularly in evaluating the efficacy of new agents. In the field of colorectal cancer, where definitive survival prolongation has recently been achieved, time to progression has now become the primary end point of randomized trials that evaluate the efficacy of newly developed agents. This change could arise from changes in the policies of regulatory authorities, and might differ between countries against different social, cultural, and economic backgrounds. Scientifically, the survival advantage of the second-line treatment has not yet been established for this disease and the prognosis for advanced disease is still limited to an MST of less than 10 months, even in recent randomized trials such as the V325 and V306 studies. Therefore, overall survival still seems to be the most reasonable primary end point. However, the median

Table 5. Recently Published and Ongoing Large Scale Randomized Phase III Trials for Advanced Gastric Cancer

Regimen	Target Accrual (patients)	Primary End Point
Western trials		
CDDP + FU *v* docetaxel + CDDP + FU	462	TTP
CDDP + FU *v* irinotecan + FU/LV	337	TTP
epirubicin + CDDP + FU *v* epirubicin + oxaliplatin + FU *v* epirubicin + CDDP + capecitabine *v* epirubicin + oxaliplatin + capecitabine	1,000	OS
CDDP + FU *v* CDDP + S-1	700	OS
Asian trials		
CDDP + FU *v* CDDP + capecitabine	300	TTP
Japanese trials		
FU *v* irinotecan + CDDP *v* S-1	700	OS
S-1 *v* S-1 + CDDP	300	OS
S-1 *v* S-1 + irinoetcan	300	OS

Abbreviations: CDDP, cisplatin; FU, fluorouracil; TTP, time to progression; LV, leucovorin; OS, overall survival.

Table 6. Summary of the Results of the V325 and V306 Trials

	V325[44]		V306[56]	
	DCF (n = 227)	CF (n = 230)	IF (n = 170)	CF (n = 163)
Response rate	37%	25%	32%	26%
Median TTP (months)	5.6	3.7	5.0	4.2
MST (months)	9.2	8.6	9.0	8.7
Grade 3/4 toxicity	81%	75%	40%	44%

Abbreviations: DCF, docetaxel + cisplatin + fluorouracil; CF, cisplatin + fluorouracil; IF, irinotecan + fluorouracil + leucovorin; TTP, time to progression; MST, median survival time.

time-to-progression in recent studies (or PFS in some studies) appears to be consistent: approximately 4 months for CF, and 5 to 6 months for modern combination regimens. Moreover, the more recent phase II studies have shown MSTs of more than 12 months. If these are confirmed in ongoing randomized trials throughout the world, the primary end point will be changed to time to progression, although quality controls of the studies and valid evaluations of time to progression are necessary.

The agents used in these randomized trials also differed between Japan and other countries. All the Japanese studies selected *S*-1 in either the control arm or the investigational arms, because this oral agent is now used most commonly in this country. The efficacy of this agent, particularly for survival advantage, has not yet been confirmed and must await the final results of the JCOG 9912 study, which compares *S*-1 with FU. In this regard, the Japanese investigators, pharmaceutical companies, and regulatory authorities may be criticized because they adopted *S*-1 as a control arm with no evidence from phase III studies. This agent also displays ethnic differences in its metabolism, leading to differential dose tolerance and toxicity. The tolerable dose of *S*-1 is substantially lower in Western patients, which has resulted in its lower acceptance in Western countries. Recent pharmacokinetic data have indicated that the polymorphisms of the *CYP2A6* gene may be responsible for such differences in FU area under the curve and discordant outcomes.[60] Despite different doses, preliminary results for the *S*-1 + CDDP combination have shown promising activity and will be followed by an ongoing randomized trial that compares it with CF in Western populations.[61] This will constitute a key trial for this agent. Capecitabine is a more globally accepted oral agent for the treatment of gastric cancer, and for colorectal cancer, although this agent is still not commercially available in Japan. When the results of Korean studies were compared with those of Western studies, there were no significant ethnic differences in outcomes with this agent between Western and Asian populations. Capecitabine combination therapies are now being evaluated in the REAL-2 and Korean studies, with a total of 1,300 patients, which is equal to the number in the Japanese studies that are evaluating *S*-1. These results will clarify the true impact of both agents and may provide comparative data. Although future direct comparisons between the effects of the two agents are desirable, such a study will be less meaningful. It seems preferable to examine the possible benefits of incorporating them with other new agents.

Another difference is evident in the results of irinotecan + CDDP therapy. In the first step of the V306 study, comparing this combination with irinotecan + FU + LV, the irinotecan + CDDP arm showed inferior survival, with an MST of only 6.9 months. The question was raised whether the JCOG study (JCOG 9912) should close accrual to the irinotecan + CDDP arm. However, the doses and schedules of this regimen differ: irinotecan (200 mg/m^2) and CDDP (60 mg/m^2) every 3 weeks in the V306 study, and irinotecan (70 mg/m^2) on days 1 and 15 and CDDP (80 mg/m^2) every 4 weeks in the JCOG study. Furthermore, the MST of this regimen in the V306 study was markedly worse than that reported in the Japanese phase II study. Moreover, the Data and Safety Monitoring Committee of the JCOG did not recommend the early termination of accrual to this arm at the interim analysis. Thus, the accrual to this arm was continued to the last patient.

Biologic differences between Western and Japanese patients might exist. Adenocarcinoma of the esophagus and gastroesophageal junction are increasing at a dramatic rate in Western countries,[62] whereas no such trend has yet been observed in Japan or East Asia.[1] Most recent Western studies have included gastroesophageal junction carcinomas in the eligibility criteria and the REAL-2 study extended this to include lower esophageal carcinomas.[57] There have also been discrepancies in selecting targeted patients. The REAL-2 study included approximately one third of patients with locally advanced disease, who have a greater chance of subsequent surgical resection. However, in Japan and Korea, a lower incidence of gastroesophageal junction carcinoma and locally advanced disease (probably due to earlier detection and more radical surgery) is evident in daily practice. These disparities may not only perturb future comparisons of the results of ongoing studies but also obstruct additional global studies.

RANDOMIZED TRIALS IN PATIENTS WITH PERITONEAL DISSEMINATION

Peritoneal metastasis is the major site of dissemination from gastric cancer. However, these patients usually have a poor general condition, impairment of oral intake, and complications such as bowel obstruction or hydronephrosis, which may retard the elimination of the agents, thereby limiting the use and doses of several agents. Patients with peritoneal dissemination are excluded from phase II studies because they usually have no measurable lesions. Therefore, specifically targeted studies should be conducted. A phase II study of the sequential combination of MTX + FU (JCOG 9603) has been carried out in patients with malignant ascites.[63] A total of 37 patients were registered. A marked decrease in ascites was observed in 13 patients (35%), including four patients (11%) in whom ascites disappeared, whereas two patients (5%) died of treatment-related toxicity. Based on these results, a phase III study comparing FU alone with MTX + FU (JCOG 0106) in patients with peritoneal dissemination has commenced and the accrual will be completed at the end of 2006. Another randomized trial undertaken by the JCOG to investigate the efficacy of paclitaxel as a second-line therapy for the treatment of this disease is now underway. These unique studies will provide a benchmark for the treatment of this disease.

FUTURE PERSPECTIVES

To date, only two triplet regimens, ECF and DCF, have demonstrated significant survival prolongation. However, the benefits seem to be marginal and the MSTs were limited to within 10 months. Survival results from the ongoing randomized trials, which will be obtained soon, are anticipated to produce MSTs that exceed 12 months. These results will determine the baseline cytotoxic regimen, although they may differ between regions or be considered as platinum-doublet or -triplet, for example. Whichever regimen is the best, new active agents will be required to achieve additional improvement. Although the number of trials has been limited so far, molecular targeting agents, particularly epidermal growth factor receptor- and vascular endothelial growth factor-targeting agents, are now being investigated. The use of gefitinib, an orally active EGFR tyrosine kinase inhibitor, has been investigated for the treatment of metastatic gastric cancer in a joint Japanese-European phase II study.[64] However, this study failed to demonstrate any activity, with a disease control rate of only 18% and

no objective response. Trastuzmab, an anti-HER2 antibody, is now being investigated in a global randomized study, predominantly in Asian and European countries, in combination with FU (or capecitabine, as oncologist's choice) + CDDP. The rationale of this study was based on the analysis of HER2 expression in surgically resected and biopsy specimens, using two commercial immunohistochemical kits and fluorescence in situ hybridization, which showed an HER2 overexpression rate of 23%.[65] Recently, promising results for bevacizumab, an anti-VEGF monoclonal antibody, in combination with irinotecan + CDDP has been reported in the United States. Shah et al[66,67] conducted a small multicenter phase II study of this combination for the treatment of metastatic disease. They reported a high response rate of 75%, although this combination was associated with a high incidence of thromboembolic events (6 of 24) and gastric perforation (2 of 24), suggesting it be used with caution. Although the efficacy of molecular targeting agents is still limited, these agents are the new hope for improving the efficacy of results, with lower toxicity than conventional cytotoxic agents. Understanding the biology of gastric cancer may result in better targets or cellular pathways that can be modified or blocked by therapeutic intervention. Improvements in clinical trial design and the introduction of molecular surrogates to clinical research will also lead to the development of better treatments. Both clinical and biologic research will become more important.

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