Table 3. Pancreatitis bundle（文献23より引用）

1. 急性膵炎診断時，診断から24時間以内，および，24～48時間の各々の時間帯で，厚生労働省重症度判定基準を用いて重症度を繰り返し評価する．
2. 重症急性膵炎では，診断後3時間以内に，適切な施設への搬送を検討する．
3. 急性膵炎では，診断後3時間以内に，病歴，血液検査，画像検査などを用いて，膵炎の成因を鑑別する．
4. 胆石性膵炎のうち，胆管炎合併例，黄疸の出現または増悪などの胆道通過障害の遷延を疑う症例には，早期のERC＋ESの施行を検討する．
5. 重症急性膵炎の治療を行う施設では，造影可能な重症膵炎症例では，初療後3時間以内に，造影CTを行い，膵不染域や病変の広がり等を検討し，CT gradeによる重症度判定を行う．
6. 急性膵炎では発症後48時間以内は，十分な輸液とモニタリングを行い，平均血圧：拡張期血圧＋（収縮期血圧－拡張期血圧）/3：65mmHg以上，尿量0.5ml/kg/h以上を維持する．
7. 急性膵炎では疼痛のコントロールを行う．
8. 重症急性膵炎では24時間以内に広域スペクトラムの抗菌薬を予防的に投与する．
9. 重症急性膵炎では，重症膵炎と診断後可及的速やかに（2日以内に）公費負担の申請書類を患者の代諾者に渡す．
10. 胆石性膵炎で胆嚢結石を有する場合には，膵炎沈静化後，胆嚢摘出術を行う．

注：ガイドライン遵守率を向上させ，患者の予後を改善するため，今回のガイドラインでは上記の臨床指標（Pancreatitis bundle）を設定した．いずれも推奨度AまたはBの内容であり，個々の施設での実状に合ったように多少の改変は可能であるがこれらの項目をすべて網羅することが必要である．特殊な状況以外では原則的にすべての項が実施されることが望ましく，診療録等に記録する．

いる．

また，ventilator bundleやsepsis bundleのようにbundleとして関連する望ましい診療内容（臨床指標）をまとめて行った場合には，個々の介入のみを行った場合よりも患者の予後が改善すると考えられている[23]．そのため，日本腹部救急医学会，日本膵臓学会，厚労省研究班などで改訂された「急性膵炎診療ガイドライン2010（第3版）」では，日本のガイドラインとしては初めて，臨床指標として「Pancreatitis bundle」が提案され（Table 3）[23][24]，ガイドラインの遵守率やその遵守の有無による患者の予後の差異を評価することが可能となった．また，このような臨床指標の提示と評価は，ガイドラインの遵守率を向上させるためのインセンティブとしても機能すると期待される．

もちろん，急性の疾患と慢性の疾患では時間軸が異なるが，各疾患の診療で施行すべき検査や治療に関してはいくつかの臨床指標をbundleという形式で明記することは，診療上行うべき内容のチェックリストとなるもので，その実施の有無が客観的に評価でき，さらには実施率の評価とともに，実施の有無と臨床効果との関連，ひいてはガイドラインの評価が可能となる．

今後は，日本のガイドラインでも作成方法のみならず，臨床指標を提示することによって，ガイドラインの遵守率やガイドラインの目的である，患者のADLや予後の変化などでもガイドラインが評価されることが必要である．

おわりに

日本でもEBMの手法を取り入れた質の高いガイドラインが作成されるようになってきた．しかし，ガイドラインの目的である，診療の変化や患者の予後の改善のためには，普及のための方策が必要である．また，ガイドラインは評価が不可欠で，まず，その実状との合致性を症例登録などによって検証することが必要であり，そのためのシステム体制の整備も急務である．ガイドラインの合致性が検証された後は，ガイドラインで提示された臨床指標，bundleなどを用いて，それらの遵守率などでガイドラインの有用性の評価が可能となる．

今後，これらの評価に基づいてガイドラインが定期的に改訂されることによってさらに臨床に合

致した望ましいガイドラインが作成され，普及し，使用され，患者の予後が改善することを期待している．

なお，この論文は厚生労働科学研究費補助金（地域医療基盤開発推進研究事業）国内版，国際版急性胆道炎診療ガイドラインの普及と検証に関する研究班（主任研究者：吉田雅博）の助成を受けた．

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（論文受領，平成22年3月2日
受理，平成22年6月8日）

Oncology
オンコロジークリニカルガイド
Clinical Guide

消化器癌化学療法

改訂3版

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消化器癌化学療法の癌種別治療戦略— 2

胃癌における化学（放射線）療法 2

胃癌の術前・術後補助化学療法

胃癌の術前・術後補助化学療法の位置づけ

● 2006年のACTS-GC試験結果によりS-1の有効性が報告されたのを受け，2010年に改訂された胃癌治療ガイドライン第3版[1]では，S-1による術後補助化学療法がわが国における標準治療と位置づけられている．

● 一方，術前補助化学療法について全生存率の改善効果を明らかに認めたというエビデンスがないため，日常診療としてはいまだ推奨されていないのが現状で，現在その点に関する臨床試験の進行結果が待たれる．

術前化学療法の意義

● 胃癌に対する従来の術前化学療法の実施は，治癒切除率の向上を目的に切除不能進行胃癌を対象とする場合が多かった．

● 近年では，切除可能であっても再発高危険群症例を対象に腫瘍の縮小や微小転移の消滅を図り，その後に原発巣や明白な転移巣を切除するという集学的治療の一環として臨床試験の範疇で施行されている．

● 以下に術前化学療法のメリットとデメリットを列挙する．

1 術前化学療法のメリット

・手術による腫瘍への血流は遮断されていないことから，薬剤の腫瘍への移行程度は良好と考える．
・術前では，手術によるPSおよび体力の低下に伴うコンプライアンスの低下は回避されているため，薬剤投与量の維持や多剤併用療法など強度のレジメン選択が可能となる．
・術前では，治験などで示されている経口抗癌剤の吸収や薬物動態の成績を利用しやすい．
・組織学的効果を確認でき，薬剤感受性の判定がより正確に可能で，術後補助化学療法のレジメン選択の参考になる．

2 術前化学療法のデメリット

・化学療法施行中に奏効性を得られぬ場合に病変が進行し，切除不能となる危険性がある．
・化学療法の有害事象により手術時期の遅延や中止を余儀なくされる場合がある．

・化学療法に伴う免疫能低下や組織変化に伴う術中・術後合併症の増加の可能性がある.
・手術までの待機期間延長に伴う経済的・精神的負担の増加が懸念される.
・術前化学療法実施の適否決定のための正確な診断が重要で，診断的腹腔鏡検査などを用いた術前進行度診断が要求される.

3 術前化学療法の適応

● 切除可能症例においては，再発の高危険群症例，切除不能症例では化学療法によるdown stagingにより，R0手術が可能となる症例があげられよう.

● ガイドラインでは，①cStageⅢA-ⅢC（cT4, cN1-2, P0, H0）症例に対し微小転移のコントロールを目的として，②R0/R1切除が可能でも予後不良となる症例として：高度リンパ節転移例，または大型3型，4型胃癌があげられ，それらに対しdown stagingを目的として，という形での具体的な適応条件をあげている[1].

4 海外における術前化学療法の臨床試験

● **MAGIC trial**[2]：英国を中心とした欧州で行われたRCTで切除可能胃癌に対し，ECF療法（エピルビシン/CDDP（シスプラチン）/5-FU）を術前，術後に3コース施行する化学療法群と手術単独群を比較した第Ⅲ相試験である．結果は化学療法群で全生存期間，無再発生存期間ともに有意な延長がみられた．本試験の問題点としては，手術単独群の3割が非治癒切除となっている点，手術死亡率が両群ともに6%および欧州とわが国における手術のqualityの違いがあり生存率などの比較は適切か否かには疑問が残る．また術後化学療法が施行されたのは55%と少ないことから，むしろ術前化学療法の有意性を示した試験として評価される.

● **EORTC study**[3]：欧州におけるRCTで，術前PLF（5-FU/ロイコボリン/CDDP）療法群と手術単独群を比較した試験である．術前化学療法群でR0切除率は82%，と手術単独群の67%に比して有意に良好であったが，無増悪生存期間に有意差は認めなかった．本試験は当初登録予定としていた360例を大幅に下回る144例のみの集積で中止されたこと，手術単独群の3割が非切除に終わったことなどが問題点といえよう.

5 わが国における術前化学療法の臨床試験

● **JCOG0001試験**[4]：わが国におけるbulky N2またはN3転移陽性胃癌（CY0）に対する多施設共同第2相試験である．CDDP/CPT-11（イリノテカン）（2～3コース）の投与後に，D2＋No.16郭清を伴う胃切除術を施行した．Primary endpointの3年生存率は27%に達したが，治療関連死亡を3例（2例：骨髄抑制，1例：術後合併症死亡）に認め，60例の登録予定を待たずに55例で登録中止となっている．このレジメンは奏効率が55%と低く，グレード3以上のneutropeniaも55%に認めたことから，以後の試験は行われていない.

● **JCOG0002試験**[5]：診断的腹腔鏡検査を施行し切除可能と診断された4型胃癌に対し，S-1単剤（2コース）の投与後に根治術を施行した第2相試験である．結果として安全性は許容

可能で，2年生存率はhistorical control群の症例における成績に対し良好であったが，15%の上乗せを見込んだ期待値には及ばなかった．

● **JCOG0210試験**[6]：大型3型，4型胃癌に対しS-1/CDDP（2コース）の投与後にD2以上の郭清を伴う胃切除を行う第Ⅱ相試験である．Primary endpointを根治切除率と治療関連死亡率とし各々73%と2%で，MSTは17.3ヵ月，3年生存率は26%であった．その良好な奏効率からS-1/CDDPは第Ⅲ相試験のレジメンとして適切であるとの判断から後述するJCOG0501試験が企画されている．

● **JCOG0405試験**[7]：Bulky N2またはN3転移陽性胃癌に対してS-1/CDDP（2コース）投与後にD3郭清を伴う胃切除術を行う第Ⅱ相試験で，JCOG0001の後継的な試験である．S-1/CDDPによる治療関連死亡はなく，JCOG0001のCPT/CDDPに比し有害事象の発生率は低率であった．Primary endpointである根治切除率は82.4%で，S-1/CDDPは高度リンパ節転移を伴う胃癌に対する暫定的な標準治療と考えられた．

● **JCOG0501試験**：JCOG0210試験にてS-1/CDDPのfeasibilityが確認されたのをもとに，切除可能な大型3型，4型胃癌に対するS-1/CDDPによるNAC群と手術単独群を比較した第Ⅲ相試験である．現在進行中で，2011年までに316症例の登録を予定し，その後3年間の追跡期間後に結果が公表される．Primary endpointは全生存期間で，secondary endpointは奏効率，根治切除率である．当初は両群とも術後補助療法は付加しない規定であったが，ACTS-GCの結果を受け現在では両群ともにS-1を1年間投与するプロトコールに改訂された．わが国における初めての術前化学療法に関する大規模臨床試験で，その結果が期待されている（**図1**）．

● **JACCRO GC01試験**[8]：cT3-T4胃癌に対するS-1/CDDPの第Ⅱ相臨床試験でfeasibilityと安全性を検証している．前述したJCOG試験との違いは1コースのみの投与で，奏効率は38.3%，根治術は79.6%に施行可能であった．

● **S-1/CDDP療法の第Ⅱ相試験（京都大学Group）**：予後不良なStageⅢ症例を対象に術前S-1/CDDP療法の有効性と安全性を評価する試験で予定症例数は49例で現在進行中である．

● **S-1/ドセタキセル療法の第Ⅱ相試験（九州大学Group）**：根治切除可能なcStage ⅢA，ⅢB，Ⅳ（T4，N2）胃癌に対する術前S-1/ドセタキセル療法の有効性と安全性を評価する第Ⅱ相試験で予定症例数は45例である．S-1の2週間投与とドセタキセルは第1，15日の分割投与としており，術前に2コースを施行するとしている．

● **COMPASS研究会**[9]：切除可能局所進行胃癌症例を対象にした術前S-1/CDDP療法とパクリタキセル/CDDP療法の有効性の比較およびそれぞれ2コースと4コースの術前投与回数の比較試験という4群設定の無作為比較試験である．Primary endpointは3年生存率で予定症例数は60～80例を予定している．

● **KDOG1001試験**：根治切除可能な大型3型，4型胃癌，bulkyN2胃癌を対象にした術前ドセタキセル/CDDP/S-1併用療法の第Ⅱ相試験である．予定症例数は40例で，現在進行中である．

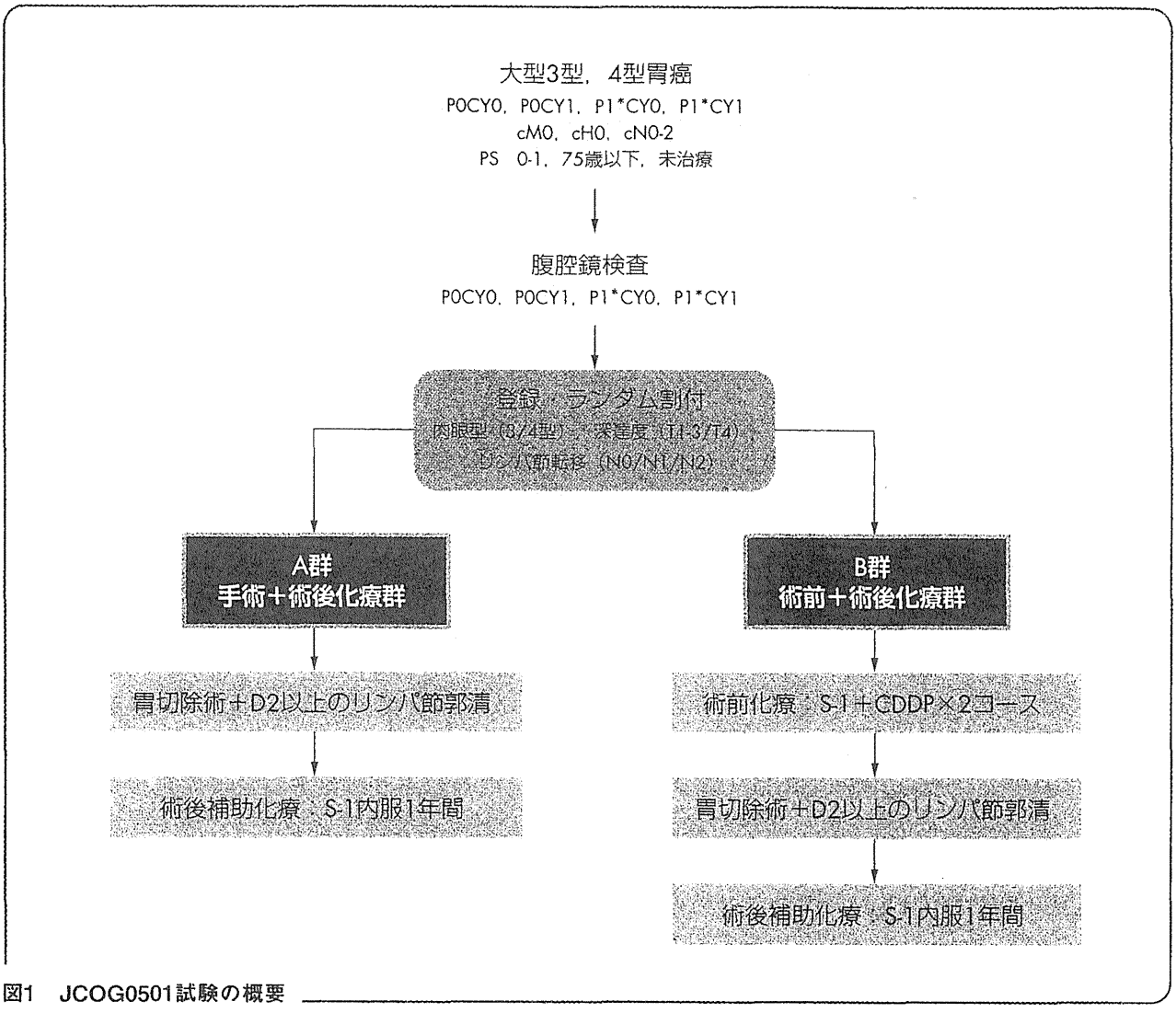

図1　JCOG0501試験の概要

＊P1：胃に近接する腹膜

（胃癌取扱い規約第12版に基づく分類）

● **DCS研究会**：局所進行T3，T4胃癌（大型3型，4型，bulkyN2，N3を除く）に対する術前ドセタキセル/CDDP/S-1併用療法の第Ⅱ相試験である．S-1を80mg/m^{2}でday1 ～ 14に，CDDPを35mg/m^{2}でday1，8に，ドセタキセルも35mg/m^{2}でday1，8に分割投与するレジメンで，1コースを4週とし2コース術前に投与するレジメンで，予定症例数は55人として現在進行中である．

● **DCS療法の第Ⅱ相試験（札幌医大Group）**：T3-4，N0-3の切除可能進行胃癌を対象にした術前ドセタキセル/シスプラチン/S-1併用療法の第Ⅱ相試験である．S-1を80mg/m^{2}でday1 ～ 14に，CDDPを60mg/m^{2}でday8に，ドセタキセルも60mg/m^{2}でday8に投与するレジメンで1コース3週を2 ～ 4コース術前に投与するレジメンで，予定症例数は30人として現在進行中である．

術後補助化学（放射線）療法の意義

● 治癒切除後の微小遺残腫瘍による再発予防を目的として行われる化学療法である．

● しかし欧米とわが国では胃癌手術のコンセプト・qualityが大きく異なるため，術後補助療法の意義も自ずと異なる．わが国ではD2郭清を伴う胃切除術が標準治療として認識されており，JCOG9501試験[10]で予防的D3郭清の効果が否定されたため，手術による局所制御としてはほぼ完成の域に達していると思われる．したがってわが国で要求される術後補助療法としては全身治療を主目的とする化学療法が主体となる．

● 一方，欧米では高度進行胃癌や肥満患者が多いことを背景に，D2郭清はD1郭清に比して合併症発生率は増加し生存率に寄与しないという認識からいまなおD0～1郭清が多く施行されているのが現状である[11,12]．そのため局所再発防止のため術後化学放射線療法による局所制御の検討が多いのが実情である．

1 海外における術後補助化学療法の臨床試験

a．術後補助化学療法

● 過去にさまざまなレジメンの術後補助化学療法と手術単独の比較試験が施行されてきたが，その有用性は示されてこなかった[13～16]．唯一補助化学療法の有用性が示されたのが先述したMAGIC試験である．

b．術後補助化学放射線療法

● **SWOG9008/INT-0116試験**[17]：stageIB～Ⅳの胃癌556症例を対象に術後5-FU/ロイコボリン＋放射線（45Gy）と手術単独群とを比較したRCTである．
・生存期間は手術単独群で27ヵ月に対し，術後化学放射線療法群で36ヵ月，ハザード比は1.35（95% CI, 1.09-1.66；$P=0.005$），再発におけるハザード比も1.52（95% CI, 1.23-1.86；$P<0.001$）と生存期間および無再発生存ともに有意に有用であるという結果であった．
・本試験の結果を受け，NCNN Clinical Practice Guidelines in Oncology™（ver.1, 2010）においてもR0手術後のT3～T4もしくはanyT，N＋症例に対する標準治療とされている．しかし本試験の問題点としてリンパ節郭清がD0（54%），D1（36%）でD2郭清は10%に過ぎないこと，またサブグループ解析ではD2郭清症例の術後補助化学療法が有意性を証明できず，わが国の標準治療の現状を考慮すると総合的所見として受容できない．

2 わが国における術後補助化学療法の臨床試験

● わが国における術後補助化学療法に関する試験は古くから行われてきたが，1980年代後半からJCOGによる手術単独群を対象としたRCTが実施されるに至った．

● **JCOG8801試験**[18]：pT1N0を除く漿膜浸潤陰性胃癌579症例を対象とした試験で，術後にMMC/5-FUを投与し，その後にUFTを18ヵ月投与し手術単独群と比較する試験である．5年生存率は手術単独群で82.9%，化学療法群で85.8%と有意差を認めなかった（$P=0.17$）．

● **JCOG9206-1試験**[19]：漿膜浸潤陰性胃癌症例を対象とした術後MFC（マイトマイシン/5-Fu/シタラビン）＋経口5-FUによる化学療法群と手術単独群を比較した試験である．5年生存

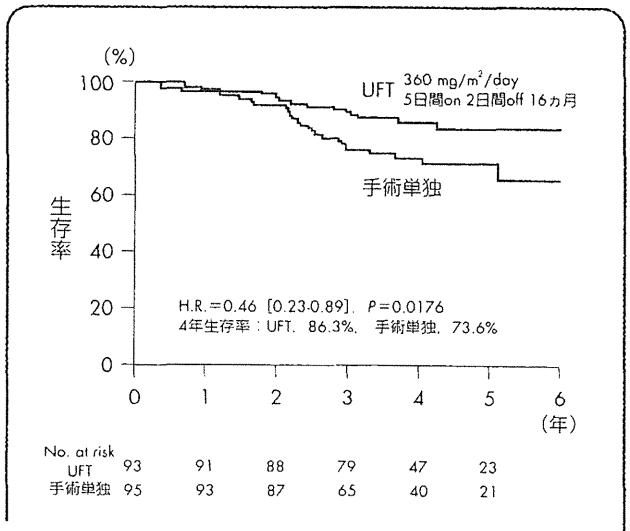

図2 NSAS-GC試験

(文献20) より引用)

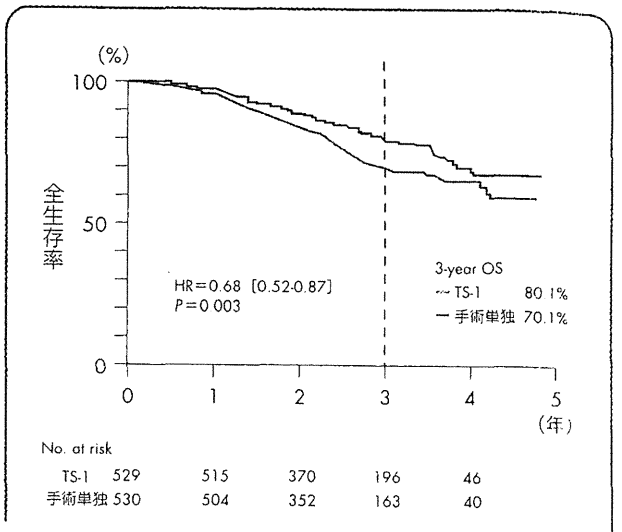

図3 ACTSS-GC試験

(文献21) より引用)

率は手術単独群で86.1%，化学療法群で91.2%と有意差は認められなかった（$P=0.13$）.

● **JCOG9206-2試験**[20]：漿膜浸潤陽性胃癌症例を対象とした術後CDDPip/FP/UFTによる化学療法群と手術単独群を比較した試験である．5年生存率は手術単独群で60.9%，化学療法群で62.0%と有意差を認めなかった（$P=0.482$）.

● **NSAS-GC試験**[21]：T2N1-2症例を対象に術後UFT高用量（360mg/m²）5日間投与，2日間休薬を16ヵ月施行し，手術単独群と比較する試験である.

・本試験は当初予定症例数500例と計画するも，190例の登録に留まったが，中間解析で有意差を認めたため早期公表された.
・5年生存率が手術単独群73%に比して，UFT群86%と有意に良好であった（$P=0.017$）**(図2)**.
・本研究のポイントは従来の試験と比較して高用量のUFT投与によるdose intensityの高さがあげられよう.

● **ACTS-GC試験**[22]
・本試験の詳細は他稿に譲るが，T1症例を除くD2以上の郭清を施行したStageⅡ，Ⅲ胃癌症例を対象にS-1：80mg/m²を原則4週投与2週休薬で1年間投与し，手術単独群と比較した第Ⅲ相試験である.
・中間解析で3年生存率が手術単独群70.1%に比してS-1投与群80.1%と有意差を認めたため（$P=0.003$），試験の中止と早期公表がなされた **(図3)**.

・本試験の5年間の追跡結果がESMO2010で公表されたが，5年生存率は手術単独群で61.1%，S-1群で71.7%（ハザード比：0.669，95% CI：0.540-0.828），5年無再発生存率は手術単独群で53.1%，S-1群で65.4%（ハザード比：0.653，95% CI：0.537-0.793）で，3年時点で報告された結果を強く裏付ける結果であった.
・本試験によりS-1の術後1年間投与がStageⅡ，Ⅲ胃癌の標準治療となり，その後のわが国における胃癌薬物療法のキードラッグとなった.

表1　SAMIT試験の概要

	UFT	S-1
手術単独	UFT単独群 UFT：267mg/m²連日投与 （4週間）×6コース	S-1単独群（対照） S-1：80mg/m²/day （2週投与1週休薬）×8コース
パクリタキセル逐次併用群	パクリタキセル→UFT逐次併用群 Weekly パクリタキセル 80mg/m² ① Day 1，8（1コース目は3週目に休薬：3週サイクル） ② Day 1，8，15（2，3コース目は4週目に休薬：4週サイクル） 2週間休薬 ③ UFT：267mg/m²連日投与 （4週間）×3コース	パクリタキセル→S-1逐次併用群 Weekly パクリタキセル 80mg/m² ① Day 1，8（1コース目は3週目に休薬：3週サイクル） ② Day 1，8，15（2，3コース目は4週目に休薬：4週サイクル） 2週間休薬 S-1：80mg/m²/day （2週投与1週休薬）×4コース

3 現在進行中の術後補助化学療法の臨床試験

● ACTS-GCの結果で留意すべき点として，N2症例では手術単独群とS-1投与群との生存率が少差である点，StageⅢA，ⅢBの3年生存率も76.2%，64.2%と決して満足のいくものではない点，腹膜再発を十分に抑制しえていない点などがあげられる．これらの改善が，今後の術後補助化学療法の臨床試験に求められる課題と思われる．

● **SAMIT試験**：漿膜浸潤陽性胃癌に対する術後補助化学療法としての，フッ化ピリミジン単独に対するパクリタキセル逐次併用による上乗せ効果の検証と共に，UFTとS-1の比較も同時に行う試験である．予定症例数は1,480例で既に症例登録は終了している．本試験によりUFTのS-1に対する非劣性の証明，パクリタキセルの併用による腹膜再発に対する効果などに関する結果が待たれる（**表1**）．

● **S-1/CDDP療法**[23]：国立がんセンターを中心にS-1/CDDP併用療法の術後補助療法としてのfeasibility試験が行われ2010年のASCO-GIで報告された．その結果，1コース目からS-1/CDDP併用療法を施行せずに，投与1コース目はS-1単独で施行し，2～4コース目はS-1/CDDP併用療法投与することで食欲不振や嘔吐などの有害事象を軽減でき，完遂率は57%から81%に改善可能であった．

● **OGSG0604試験**[24]：StageⅢ胃癌に対する術後S-1/ドセタキセル療法の第Ⅱ相試験で，S-1/ドセタキセルを4コース施行し，その後に術後1年までS-1単剤を投与するレジメンである．S-1/ドセタキセルを4コース投与可能であったのは77.4%で，認容可能なレジメンであると報告している．

● 今後は2011年より切除不能進行・再発胃癌に承認されたカペシタビンや既に大腸癌で承認されているオキサリプラチンなどの新規抗癌剤，同じく本年承認されたトラスツズマブなどの分子標的薬などの出現・導入によりさまざまな臨床試験が展開されることが予想される．

（信岡隆幸／平田公一）

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オンコロジークリニカルガイド
消化器癌化学療法

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定価（本体 5,500 円＋税）

2007年11月 5日　1版1刷
2009年11月 1日　2版1刷（改題）
2010年 6月15日　　2刷
2011年11月 5日　3版1刷

編　者　大村 健二（おおむら けんじ）
　　瀧内 比呂也（たきうち ひろや）

発行者　株式会社 南山堂
　　代表者 鈴木 肇

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振替口座　00110-5-6338

ISBN 978-4-525-42053-6　　Printed in Japan

A4205310301-A

Journal of Surgical Oncology 2011;104:45–52

High-Risk Stage II Colon Cancer After Curative Resection

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Objectives: This study was designed to clarify which attributes of stage II colon cancer are associated with tumor recurrence and survival after curative resection, and the effects of adjuvant chemotherapy (ACT).

Methods: We retrospectively reviewed outcomes and clinicopathological characteristics of 1476 patients with stage II colon cancer who underwent curative resection.

Results: Of 1476 patients, 204 (13.8%) developed recurrence. Macroscopic type, serum CA19-9 levels, venous invasion, emergency operation, and postoperative ileus were independently associated with overall recurrence. Carbohydrate antigen (CA)19-9 levels, the number of dissected lymph nodes (LN), sex, age, ACT, emergency operation, venous invasion, and macroscopic type were independently associated with poor prognosis. Prognosis was significantly better in patients who received ACT than in those who did not. Among patients with extensive venous invasion, those with fewer than 13 dissected LNs, male patients, and patients >50 years old, the prognosis was significantly better in patients who received ACT than in those who did not.

Conclusions: ACT for stage II colon cancer is recommended to improve the prognosis of patients with extensive venous invasion, patients with fewer than 13 dissected LNs, patients >50 years old, and male patients, particularly patients with more than two of these risk factors.
J. Surg. Oncol. 2011;104:45–52. © 2011 Wiley-Liss, Inc.

KEY WORDS: **colon carcinoma; curative resection; prognostic factors; adjuvant chemotherapy**

INTRODUCTION

Colorectal cancer is the second-leading cause of cancer mortality in the United States [1], and the third-leading cause in Japan [2]. Surgical treatment is considered the best approach to cure colorectal cancer, but recurrence still occurs according to the stage of disease after surgery. The most important prognostic indicator for survival in locally advanced colon cancer is tumor stage, which is determined by the depth of invasion, the number of lymph nodes (LNs) involved and the presence of distant metastases, as in the American Joint Committee on Cancer (AJCC)-TNM staging criteria [3]. Thirty to forty percent of colon cancers are diagnosed as AJCC stage II disease at resection [1,4]. These patients have a relatively good prognosis after surgery alone with 5-year survival rates of approximately 80% [5,6].

The goal of adjuvant chemotherapy (ACT) after curative resection of early-stage colon cancer is to eliminate microscopic local or metastatic disease and thus reduce the risk of tumor recurrence and improve survival rate. However, ACT has not been conclusively shown to have a significant benefit on survival because of conflicting results in the literature [7]. Therefore, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines do not recommend the routine use of ACT for stage II colon cancer patients. On the other hand, the ASCO

Conflicts of interest: None

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Received 12 October 2010; Accepted 23 February 2011

DOI 10.1002/jso.21914

Published online 17 March 2011 in Wiley Online Library (wileyonlinelibrary.com).

and NCCN guidelines do state that ACT could be considered for patients with high-risk features, including T4 tumors leading to obstruction, perforation, and for patients with fewer than 12 LNs [8,9]. However, the high-risk features of colon cancer have not yet been determined.

Accordingly, it is important to identify which patients with stage II colon cancer are at high risk of recurrence and have poor prognosis following curative resection to provide an effective and cost-beneficial follow-up program. Therefore, the principle aim of the present study was to identify which attributes of stage II colon cancer are associated with tumor recurrence and survival after curative resection in a large-scale retrospective multicenter study. We also used this opportunity to investigate the effects of adjuvant chemotherapy (ACT) after curative surgery.

PATIENTS AND METHODS

Between January 1991 and December 1996, 1476 patients with stage II colon cancer underwent curative resection at 15 hospitals, which were members of the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer. This included all consecutive patients with stage II colon cancer treated during the study period. The patients were monitored as outpatients at each of the participating hospitals until December 2003, by which time 8.1% (119 patients) of the patients were lost to follow-up. The patients did not receive preoperative radiotherapy or chemotherapy. Cancers associated with ulcerative colitis, Crohn disease, hereditary nonpolyposis colorectal cancer, or familiar adenomatous polyposis were excluded from the analysis. Complete dissection of all regional lymph nodes, including pericolic, intermediate, and major lymph nodes according to the Japanese classification of colorectal carcinoma [10], was performed in all patients. The major lymph nodes were dissected around the root of the feeding artery regardless of any division of the feeding artery. The colon was divided at least 10 cm proximally and distally from the tumor, and at a minimum distance of 10 cm on the proximal side and 6 cm on the distal side for rectosigmoid colon cancer. No evidence of tumor tissue was found at the proximal, distal, and radial margins in any of the patients. Preoperative investigations included barium enema, colonoscopy, chest X-ray, ultrasonography (US), computed tomography (CT) of the liver, and blood levels of carcinoembryonic antigen (CEA) and/or carbohydrate antigen 19-9 (CA19-9). Most institutions established a follow-up examination period exceeding 5 years. The follow-up system consisted of measurement of serum tumor markers every 3 months for the first 3 years and then every 6 months for the next 2 years, hepatic imaging (US and/or CT) and chest X-rays every 6 months, pelvic CT for rectal cancer every year, and colonoscopy every 1–2 years. Data concerning additional treatments, recurrence, and prognosis were retrospectively collected. Preoperative ileus was defined as cases needing the insertion of a long intestinal tube or the creation of a colostomy before tumor resection. Postoperative ileus was defined as cases needing the insert of a long intestinal tube, delays in starting the diet because of abdominal symptoms such as abdominal fullness, nausea, and vomiting, which were thought to be caused by disturbed passage or peristaltic abnormality, or to stop the diet after the initial oral intake. ACT comprised oral 5-FU derivatives such as UFT (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) or 5'DFUR, in all of the patients that received ACT (611 cases). Continuous infusion of 5-FU was performed in 36 patients, and bolus infusion of 5-FU and leucovorin was used in three patients. In these patients, the initial infusion of 5-FU was followed by the administration of oral 5-FU derivatives until at least 12 months after surgery. No significant differences were found in the distribution of ACT among each factor measured. At that time, oral 5-FU derivatives were routinely administrated until at least 12 months after surgery in Japan based on the results of several studies of Japanese patients [11–13]. The mean ± standard deviation duration of ACT administration was 12.0 ± 11.8 months. Based on histological findings, all tumors were classified as either well differentiated, which included well and moderately differentiated adenocarcinoma, and poorly differentiated, which included mucinous carcinoma (32 patients), signet ring cell carcinoma (2 patients), and poorly differentiated adenocarcinoma (39 patients). Tumor location, macroscopic type, venous invasion, and lymphatic invasion were described according to the Japanese classification of colorectal carcinoma [10]. The rectosigmoid was defined as the portion of the large intestine that is located between the promontory and the inferior border of the second sacral vertebra [10], corresponding to about 12 cm from the anal verge [14], and was included in this analysis. Based on macroscopic findings, all tumors were classified as either a macroscopic pushing type, which corresponds to tumors with a clear margin, and the macroscopic infiltrating type, which corresponds to tumors with an infiltrating margin. Based on microscopic findings (magnification, ×4), vessel invasion was histologically classified according to the severity of venous or lymphatic invasion as either slight (0–3 affected vessels) or extensive (>3 affected vessels) [10]. Emergency operation was indicated for perforation or obstructive ileus caused by the tumor. Resection was considered for recurrence in the absence of any medical contraindications to surgery when the recurrence was technically resectable and no metastases in other organs were present. We retrospectively determined which factors were associated with recurrence and prognosis in stage II colon cancer.

Statistical Analysis

Statistical analysis was performed using Statview version 5.0 software (Abacus Concepts, Inc, Berkeley, CA). All data are expressed as the mean ± standard deviation. The χ^2 test or Fisher's exact probability test was used to compare recurrence rates. Logistic regression analysis was performed to further evaluate the factors associated with the recurrence found to be significant in χ^2 tests or Fisher's exact probability test at a level of $P < 0.05$ to identify which factors were independently associated with recurrence. Survival rates were calculated by the Kaplan–Meier method and compared by the log-rank test and the generalized Wilcoxon test. Survival analysis was done using the stepwise forward Cox regression model for factors that were found to be significant by the log-rank test or the generalized Wilcoxon test at a level of $P < 0.05$ to determine which factors were independently associated with survival. Values of $P < 0.05$ were considered significant for all analyses.

RESULTS

Cancer Recurrence

Recurrence was discovered in 204 patients (13.8%). The median time to recurrence after the initial resection for colon cancer was 17.5 ± 24.3 months. The median duration of follow-up of patients with recurrence and those without recurrence was 52.5 ± 41.7 and 101.5 ± 43.4 months, respectively. The recurrence rates according to the clinicopathological categories are shown in Table I. Tumor location in the rectosigmoid colon, macroscopic infiltration type [10], ≤12 dissected LNs, well-differentiated type, extensive venous invasion, >2-fold elevations in serum CEA levels, high serum CA19-9 levels relative to the normal limit, emergency operation, postoperative ileus, and postoperative chemotherapy were significantly associated with an increased recurrence rate. On the other hand, age, sex, circumference, and diameter of the tumor, depth of invasion, lymphatic invasion, perforation during surgery, leakage and preoperative ileus were not significantly associated with recurrence. Logistic regression analysis of factors that were

TABLE I. Recurrence Rates According to Clinicopathological Factors

Variable	Category	Patients with recurrence (%)	Patients without recurrence (%)	Total	*P* value
Age	≤50	33(18.4)	145(81.0)	179	0.06
	>50	171(13.2)	1105(85.3)	1296	
Sex	Men	125(14.2)	747(84.8)	881	0.62
	Women	79(13.3)	504(84.7)	595	
Location	Rs	46(19.3)	188 (79.0)	238	0.007
	Colon	158(12.8)	1062(85.9)	1237	
Macroscopic type	Pushing type	173(13.0)	1141(85.6)	1333	0.003
	Infiltrating type	30(23.4)	96(75.0)	128	
Circumference	≥80%	100(14.6)	570(83.2)	685	0.42
	<80%	58(13.1)	378(85.5)	442	
Diameter (cm)	≤5	87(13.6)	543(85.1)	638	0.68
	>5	114(14.2)	678(84.2)	805	
Number of dissected LN	≤12	74(17.8)	338(81.4)	415	0.005
	>12	120(12.5)	825(85.7)	963	
Histology[a]	Well	199(14.2)	1181(84.5)	1398	0.03
	Poorly	5(6.8)	65(89.0)	73	
Depth of invasion	<T3	182(13.3)	1164(85.3)	1364	0.06
	T4	22(19.6)	87(77.7)	112	
Lymphatic invasion	Slight	166(13.4)	1059(85.3)	1242	0.24
	Extensive	38(16.8)	184(81.4)	226	
Venous invasion	Slight	156(12.7)	1063(86.4)	1230	0.005
	Extensive	47(19.8)	190(75.95)	237	
Serum levels of CEA	≤NL × 2	130(12.3)	906(86.0)	1053	0.003
	>NL × 2	48(19.8)	191(78.6)	243	
Serum levels of CA19-9	≤NL × 1	143(12.95)	950(85.8)	1107	0.001
	>NL × 1	32(25.8)	89(71.8)	124	
Emergency operation	+	12(38.7)	19(61.3)	31	0.0001
	−	191(13.2)	1231(85.3)	1443	
Perforation during surgery[a]	+	2(28.6)	5(71.4)	7	0.26
	−	200(13.7)	1244(84.9)	1465	
Leakage[a]		7(26.9)	19(73.1)	26	0.06
	−	194(13.4)	1229(85.1)	1444	
Preoperative ileus	+	14(21.5)	51(78.5)	65	0.07
	−	188(13.4)	1198(85.1)	1407	
Postoperative ileus	+	15(24.2)	47(75.8)	62	0.02
	−	187(13.3)	1201(85.2)	1409	
Postoperative ChT	+	101(16.5)	505(82.7)	611	0.01
	−	103(11.9)	745(86.2)	864	

LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon; NL, normal limit.

[a]Fisher's exact probability test; other analyses were performed by χ test. Macroscopic type, venous invasion, and lymphatic invasion are defined according to the Japanese classification of colorectal carcinoma.

significantly associated with recurrence in χ^2 tests and Fisher's exact probability test revealed that macroscopic type, venous invasion, serum CA19-9 levels, emergency operation, and postoperative ileus were independently associated with overall recurrence (Table II).

Prognosis after Surgery

The 5-year survival rate of all patients with stage II colon cancer was 83.7%. The overall 5-year survival rate according to clinicopathological categories is shown in Table III. Patients within the

TABLE II. Multivariate Regression Analysis for Overall Recurrence of Stage II Colon Cancer

		HR	95% CI	*P* value
1. Macroscopic type	Pushing vs. infiltrating	0.382	0.226–0.645	0.0003
2. Serum levels of CAI9–9	≤1× vs. >1×	2.313	1.438–3.721	0.0005
3. Venous invasion	Slight vs. extensive	1.847	1.204–2.834	0.005
4. Emergency operation	+ vs. −	2.856	1.206–6.764	0.017
5. Postoperative ileus	+ vs. −	2.354	1.143–4.848	0.020
6. Location	Colon:Rs	0.685	0.465–1.010	0.056
7. Serum levels of CEA	≤2× vs. >2×	1.404	0.927–2.127	0.11
8. Number of dissected LN	≤12 vs. >12	0.742	0.507–1.084	0.12
9. Histology	Well vs. poorly	1.679	0.572–4.931	0.35
10. Postoperative ChT	+ vs. −	1.046	0.733–1.493	0.80

HR, hazard ratio; CI, confidence interval; LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon.

following groups had significantly worse prognosis based on the log rank test and/or generalized Wilcoxon test: >50 years old, males, tumor located in the rectosigmoid colon, macroscopic infiltration-type tumors, tumor circumference >80% of the intestinal circumference, T4 tumor, extensive lymphatic/venous invasion, ≤12 dissected LNs, 2-fold higher than normal serum CEA levels or high serum CA19-9 levels, emergency operation, and leakage. On the other hand, postoperative chemotherapy improved prognosis. Diameter, histology, perforation during surgery, preoperative ileus, and postoperative ileus were not significantly associated with overall survival. Multivariate Cox regression analysis of factors associated with prognosis on log rank tests and generalized Wilcoxon tests revealed that the serum CA19-9 levels, the number of dissected LNs, sex, age, emergency operation, venous invasion, and macroscopic type were independently associated with overall prognosis (Table IV). Postoperative chemotherapy was independently associated with improved prognosis.

Effects of ACT on Recurrence and Prognosis

The recurrence rate was significantly higher in patients who received ACT (16.5%) than in those who did not (11.9%) (Table I). Conversely, the 5-year survival rate was significantly better in patients who received with ACT (86.0%) than in those who did not (82.3%) (Table III). Furthermore, multivariate Cox regression analysis revealed that ACT was independently associated with overall prognosis in stage II colon cancer (Table IV).

There was no significant difference in the duration of ACT between patients with (12.0 ± 8.9 months) and without (12.0 ± 12.2 months) recurrent diseases. The disease-free time after surgery was 21.5 ± 24.0 months among patients who received ACT versus 16.1 ± 20.1 months in patients who did not. However, there was no significant difference in disease-free time between the two groups. The clinicopathological characteristics of patients with or without ACT are summarized in Table V. The frequencies of young patients, larger number of dissected LNs, preoperative ileus, and high serum levels of CEA and CA19-9 were significantly greater in patients who received ACT than in those who did not. Recurrence sites included the liver (49 patients), lung (21 patients), and local sites (15 patients) in 101 cases who received ACT, and in the liver (53 patients), lung (19 patients), and in local sites (14 patients) of 103 patients who did not receive ACT. There were no significant differences in the numbers of patients for each recurrent site between patients who did or did not receive ACT. Surgery for recurrent disease was performed in

TABLE III. Clinicopathologic Variables and Overall Survival of Stage II Colon Cancel

Variable	Category	*n*	5-year survival (%)	*P* value log rank/Wilcoxon
Age	<50	179	87.1	0.02/0.07
	>50	1296	83.3	
Sex	Men	881	81.5	0.004/0.002
	Women	595	87.1	
Location	Rs	1237	85.0	0.03/0.08
	Colon	238	79.0	
Macroscopic type	Pushing type	1333	85.7	0.07/0.01
	Infiltrating type	128	72.6	
Circumference	≥80%	685	81.1	0.03/0.03
	<80%	442	87.3	
Diameter (cm)	≤5	638	85.1	0.10/0.13
	>5	805	82.0	
Number of dissected LN	≤12	415	78.8	0.0001/0.001
	>12	963	85.6	
Histology	Well	1398	82.6	0.89/0.89
	Poorly	73	84.2	
Depth of invasion	<T3	1364	85.4	0.02/0.006
	T4	112	74.4	
Lymphatic invasion	Slight	1242	85.1	0.05/0.04
	Extensive	226	81.1	
Venous invasion	Slight	1230	85.4	0.01/0.01
	Extensive	237	80.7	
Serum levels of CEA	≤NL × 2	1053	85.3	0.005/0.002
	>NL × 2	243	76.0	
Serum levels of CAI 9-9	≤NL × 1	1107	85.3	0.0001/0.0001
	>NL × 1	124	69.5	
Emergency operation	+	31	59.0	0.002/0.0001
	−	1443	85.1	
Perforation during surgery	+	7	71.4	0.66/0.53
	−	1465	84.9	
Leakage	+	26	66.9	0.05/0.02
	−	1444	84.9	
Preoperative ileus	+	65	70.4	0.10/0.02
	−	1407	85.2	
Postoperative ileus	+	62	87.9	0.40/0.42
	−	1409	85.2	
Postoperative ChT	+	611	86.0	0.006/0.006
	−	864	82.3	

LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon; NL, normal limit.
Macroscopic type, venous invasion, and lymphatic invasion are defined according to the Japanese classification of colorectal carcinoma.

TABLE IV. Multivariate Regression Analysis for Overall Survival of Stage II Colon Cancer

		HR	95% CI	*P* value
1. Serum CA19-9 levels	≤1× vs. >1×	2.029	1.437–2.864	0.0001
2. Number of dissected LNs	≤12 vs. >12	0.604	0.459–0.795	0.0003
3. Sex	Male vs. female	1.504	1.148–1.970	0.003
4 Age	≤50 vs. >50	2.173	1.281–3.687	0.004
5. Postoperative ChT	+ vs.−	0.682	0.523–0.891	0.005
6. Emergency operation	+ vs. −	2.626	1.296–5.323	0.007
7. Venous invasion	Slight vs. massive	1.444	1.068–1.953	0.017
8. Macroscopic type	Pushing vs. infiltrating	0.624	0.412–0.944	0.026
9. Serum levels of CEA	≤2× vs. >2×	1.342	0.995–1.809	0.054
10. Leakage	+ vs. −	1.878	0.918–3.845	0.08
11. Circumference	+ vs. −	1.234	0.856–1.779	0.24
12. Lymphatic invasion	Slight vs. Massive	1.216	0.862–1.715	0.27
13. Depth of invasion	−T3 vs. T4	0.822	0.536–1.261	0.37
14. Preoperative ileus	+ vs. −	1.297	0.668–2.518	0.44
15. Location	Colon vs. Rs	1.052	0.807–1.370	0.71

HR, hazard ratio; CI, confidence interval; LN, lymph node; ChT, chemotherapy; Rs, rectosigmoid colon.

TABLE V. Background of Patients With or Without Postoperative Chemotherapy

Variable	Category	With chemotherapy	Without chemotherapy	*P*
Age		63.0 ± 10.4	66.0 ± 11.8	0.0001
Location	Colon/Rs	511/100	726/138	0.84
Sex	Male/female	368/243	513/351	0.74
Histology	Well/poorly	582/29(0)	814/45 (5)	0.23
Macroscopic type	Pushing/infiltrating	549/56 (6)	783/72 (9)	0.34
Depth of invasion	<T3 T4	562/49	801/63	0.60
Lymphatic invasion	Slight/massive	518/87(6)	724/138(2)	0.61
Venous invasion	Slight/massive	229/423(5)	290/570(4)	0.12
Number of dissected LN		23.5 ± 18.3	20.9 ± 14.3	0.002
Serum levels of CEA	≤2/>2	414/108(89)	645/129(90)	0.004
Serum levels of CA19-9	≤1/>1	369/53(189)	636/71(157)	0.00001
Postoperative ileus	+/−	33/574(4)	29/834(1)	0.054
Emergency operation	+/−	14/586(1)	17/846 (1)	0.64
Diameter		15.5 ± 2.4	40.0 ± 2.4	0.57
Circumference	≥80%/<80%	200/297(114)	242/387(235)	0.051
Preoperative ileus	+/−	39/569(3)	25/838(1)	0.001
Leakage	+/−	9/597(5)	17/846(1)	0.48
Perforation during surgery	+/−	3/605(3)	4/859(1)	0.94

LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon. Numbers in parentheses represents the number of patients with unknown data.

56/101 patients (48.7%) who received ACT, and in 56/103 patients (44.4%) who did not receive ACT, which was not significantly different. Similarly, there were no significant differences in the frequency of surgery for recurrent disease for each recurrent site between patients who did or did not receive ACT. The 5-year survival rate of patients with recurrent diseases was 52.0% in patients who received ACT versus 42.9% in patients who did not receive ACT. There was no significant difference in the prognosis of patients with recurrent diseases between those who received ACT and those who did not. However, the 5-year survival rate of patients without recurrent diseases was 92.4% for those who received ACT versus 89.4% for patients who did not (log rank: $P = 0.003$; Wilcoxon $P = 0.005$). Regarding patients who were deemed to be at high risk of recurrence based on the predictive factors identified in Table II, there was no significant difference in the overall frequency of recurrence between patients who did or did not receive ACT. Comparisons of the prognosis between patients who did or did not receive ACT according to each independent prognostic factor (Table IV) are shown in Table VI. The prognosis was significantly better for patients who received ACT than for those who did not if they had extensive venous invasion, had ≤12 dissected LNs, were male patients or were >50 years old (Table VI). Survival curves according to the number of independent factors are shown in Figure 1. When the proximal colon was defined as sites between the cecum and transverse colon, the proximal colon was significantly more frequently involved in patients with one independent factor (45.5%) than in patients with more than one independent factor (34.1%; $P = 0.0001$). There were no significant differences in patient characteristics, except for the independent factors among the groups of patients. None of the patients had more than five independent prognostic factors. All of the patients without any of these independent prognostic factors survived for longer than 5 years. The 5-year survival rate was 88.6% in patients with one independent factor. Survival was significantly better in patients with no independent prognostic factors than in patients with one independent prognostic factor ($P = 0.036$). Prognosis worsened with increasing number of independent prognostic factors ($P = 0.008$ for 2 and 3 factors; $P = 0.007$ for 3 and 4 factors). The survival curves for patients who did or did not receive ACT

TABLE VI. Five-Year Survival Rate of Patients With or Without Postoperative Chemotherapy Among Patients the Poor Prognosis

	With ChT		Without ChT		
	N	5SR	N	5SR	*P*
Macroscopic type (infiltrating type)	56	76.2%	72	68.5%	0.42
Venous invasion (massive invasion)	90	83.5%	147	78.7%	0.038
Serum CA19-9 levels (<1)	53	72.9%	71	67.8%	0.57
Number of dissected LNs (≤12)	178	83.4%	237	75.2%	0.005
Emergency operation	14	72.2%	17	43.1%	0.21
Male	368	86.2%	513	77.5%	0.0001
Age >50 years	513	86.3%	783	81.4%	0.001

ChT, chemotherapy; 5SR, 5-yeasr survival rate; LN, lymph node.

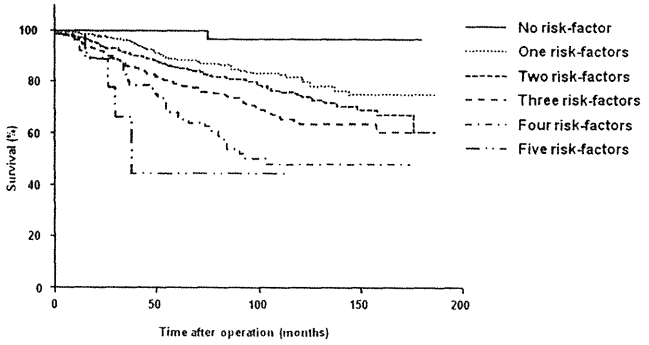

Fig. 1. The prognosis of stage II colon cancer worsened with increasing number of independent prognostic factors ($P = 0.036$ for 0 or 1 factors; $P = 0.008$ for 2 or 3 factors; $P = 0.007$ for 3 and 4 factors).

according to the number of independent prognostic factors are shown in Figure 2. Among patients with more than one independent prognostic factor, the 5-year survival rate was significantly better in patients who received ACT (86.1%) than in those who did not (78.0%) (Fig. 2). However, among patients with only one factor, the 5-year survival rate was significantly worse in those who received ACT (83.3%) than in those who did not (93.0%) (Fig. 2). Among patients with one prognostic factor, significantly more patients with high serum levels of CA19-9 received ACT than did not, although there were no significant differences in the characteristics between patients who received ACT and those who did not.

DISCUSSION

The recurrence rate of stage II colon cancer was reported to range from 7.9 to 22%, while the 5-year survival rate was reported to range from 75 to 92% [5,6,15]. In the present study, the corresponding rates were 13.8 and 83.7%, respectively. Clearly, patients with stage II colon cancer generally show a relatively low recurrence rate and good prognosis after surgery. However, some patients with stage II colon cancer do develop recurrence and a poor prognosis as frequently as that of stage III colon cancer, representing high-risk for recurrence and poor prognosis. The recurrence rate of Dukes C colon cancer was reported to be 24.3% [16], while the 5-year survival rate of Dukes C colon cancer in patients with fewer than four positive nodes was reported to be about 80% [17,18]. In the present study, macroscopic infiltrating-type tumors, high serum CA19-9 levels, extensive venous invasion, emergency operation, and postoperative ileus were independently associated with high risk of recurrence for stage II colon cancer. Meanwhile, high serum CA19-9 levels, ≤12 dissected LNs, males, >50 years old, emergency operation, extensive venous invasion, and macroscopic infiltrating-type tumors were independently associated with poor overall prognosis. The recurrence and 5-year survival rates of patients with these factors seemed to be

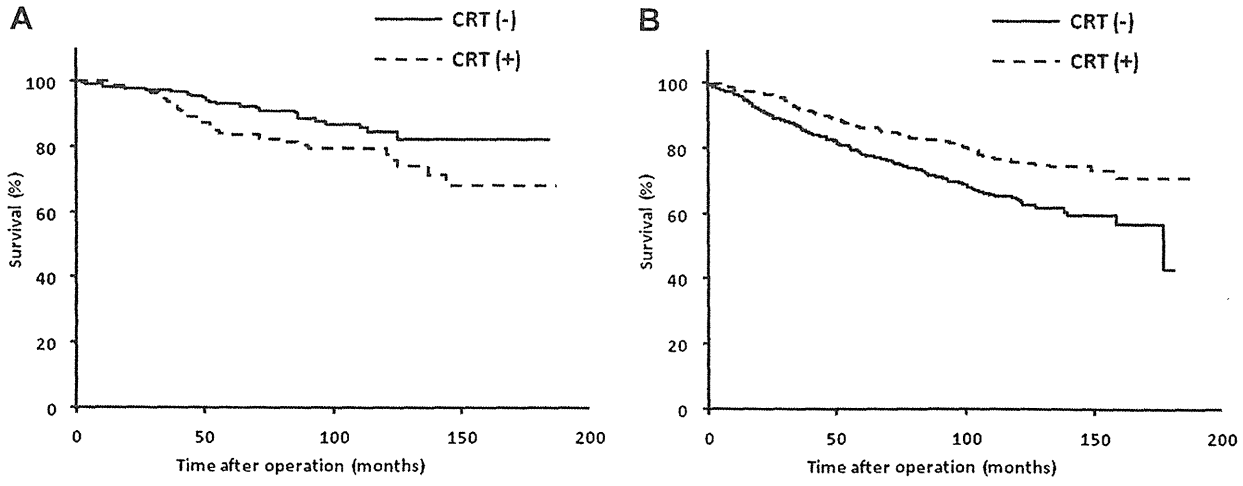

Fig. 2. (**A**) Among patients with only one independent prognostic factor, the 5-year survival rate was significantly worse in patients who received ACT (83.3%) than in those who did not receive ACT (93.0%). (**B**) Among patients with more than one independent prognostic factor, the 5-year survival was significantly better in patients who received ACT (86.1%) than in those who did not receive ACT (78.0%).

similar to or worse than those for stage III colon cancer. Therefore, patients with these factors were considered to have a high risk of recurrence and poor prognosis. On the other hand, all of the patients without any of these prognostic factors survived for longer than 5 years. Consequently, ACT is recommended for use in stage III colon cancer [7]. The results of our study also suggest that patients with stage II colon cancer at high of recurrence or poor prognosis can also be considered as candidates for ACT.

Postoperative ACT was independently and favorable associated with overall prognosis, suggesting that 5-FU-based postoperative ACT is an important approach that can improve the prognosis of stage II colon cancer. A survival benefit of FU-based ACT in stage II colon cancer was also reported by the Adjuvant Colon Cancer Endpoints (ACCENT) group with a similar follow-up duration to that in the present study [19]. However, ACT is not recommended for routine use in stage II colon cancer patients because the overall survival benefit of ACT has not been clearly demonstrated in stage II colon cancer [6,20]. The QUASAR Collaborative Group reported that chemotherapy with fluorouracil acid and folinic acid reduced the relative risk of recurrence for 2 years after surgery in patients with stage II colon cancer, although it did not improve prognosis [21]. ACT may be administered to patients with high-risk stage II colon cancer as well as stage III colon cancer. The ASCO and the NCCN guidelines recommend considering ACT for patients with stage II colon cancer patients and the presence of high-risk features, including T4 tumors leading to obstruction, perforation, and fewer than 12 LNs [8]. The National Surgical Adjuvant Breast and Bowel Project group revealed a survival benefit of ACT in stage II colon cancer in patients with poor prognosis, namely those with T4 tumor and those with obstruction or perforation [22]. However, T4 tumors were not independently associated with recurrence or prognosis in our study, although emergency operation for perforation or obstruction was a significant independent prognostic factor. The present study also revealed that ACT should be considered for stage II colon cancer in patients with macroscopic infiltrating-type tumors, high serum CA19-9 levels, extensive venous invasion, and postoperative ileus because of a high risk of recurrence. Furthermore, male patients, patients $\leq$50 years old, and those with $\leq$12 dissected LNs will also benefit from ACT because of the poor prognosis associated with these factors. Several other predictive factors have been proposed recently, including microsatellite instability (MSI), 18q deletions, k-ras mutations, TP53, and TS gene expression, of which MSI seems to be a particularly promising factor. Tumors with high MSI are associated with more favorable outcome while fluoropyrimidine-based chemotherapy seems to have limited efficacy and is sometimes detrimental in patients with such tumors [9].

The present study showed that the prognosis was significantly better in patients who received ACT than in those who did not. This was particularly true in patients without recurrent diseases, despite the high recurrence rate in patients who received ACT. The disease-free time was longer, the rate of surgery for recurrent disease was higher, and the survival of the patients with recurrence was better among those who received ACT than among those who did not, although these differences did not reach statistical significance. These results in patients with recurrent diseases, as well as the significantly better prognosis in patients who received ACT than in patients who did not receive ACT among those without recurrent diseases, could explain why the prognosis was significantly better in patients who received ACT, despite the higher recurrence rate in these patients. ACT was also independently associated with overall prognosis. ACT was more frequently administered to younger patients, patients with high serum levels of CEA and CA19-9, and patients with preoperative ileus, a group of patients representing high risk of recurrence and poor prognosis. This implies that ACT was administered in accordance with the correct criteria at each institute, and may also explain why recurrence was more common in patients who received ACT than in those who did not. On the other hand, there was no significant difference between patients who did or did not receive ACT in terms of the frequency of overall recurrence among patients considered to be at high risk of recurrence. Meanwhile, among patients considered to have a poor prognosis group, namely those with extensive venous invasion, $\leq$12 dissected LNs, males, and > 50 years old, survival was significantly better in those who received ACT than in those who did not. Thus, ACT seemed to improve the prognosis of these patients with poor prognosis, particularly those with more than one of these prognostic factors. ACT also significantly improved the prognosis of patients with more than one of these independent prognostic factors. The reason why the prognosis was significantly worse in patients who received ACT than in those who did not for patients with only one of these independent prognostic factors is currently unclear. However, the proximal colon, in which high MSI is more common than in the distal colon, was significantly more frequently involved in patients with one independent prognostic factor than in patients with more than one factor. Furthermore, among patients with one factor, significantly more patients who received ACT than those who did not had high serum CA19-9 levels, another independent factor associated with poor prognosis. This may explain why the prognosis was significantly worse among patients with only one prognostic factor who received ACT than those who did not receive ACT. Based on these findings, it does not seem to be appropriate to administer ACT in patients with only one of these prognostic factors.

Oral 5-FU derivatives used in ACT, such as 5-FU, UFT, or 5'DFUR, were the most commonly used treatments for stage II colon cancer in Japan during the period studied. 5-FU- and leucovorin-based infusional regimens, such as FOLFOX4, mFOLFOX6, and FLOX, and other oral 5-FU derivatives such as capecitabine and UFT +Uzel, have been used in several studies that demonstrated the effectiveness of ACT in stage III colon cancer after curative resection [23–30]. The present study does not downplay the efficacy of all 5-FU-based regimens as ACT for treat stage II colon cancer. Rather, the results suggest that fluoropyrimidine-based ACT might be appropriate for patients with extensive venous invasion, patients with $\leq$12 dissected LNs, males, and patients >50 years old.

Overall, the results presented here suggest that factors concerned with recurrence and poor prognosis should be taken into account in the management of patients with stage II colon cancer after curative surgery. Large-scale randomized clinical trials are now required to provide definitive conclusions regarding the indications for ACT in stage II colon cancer.

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Surg Today (2011) 41:39–47
DOI 10.1007/s00595-010-4337-6

SURGERY TODAY

Review Article

Laparoscopic Hepatectomy: A Systematic Review, Meta-Analysis, and Power Analysis

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Abstract

Purpose. A previous meta-analysis study demonstrated that bleeding and the duration of the hospital stay following laparoscopic hepatectomy (Lap) were significantly smaller and shorter, respectively, than for patients undergoing an open approach (Op). The aim of the present study was to re-evaluate perioperative variables and adverse outcomes in patients undergoing Lap versus (vs) Op after 2000.

Methods. A PubMed and Ovid Medline search identified clinical studies that compared the outcomes of Lap vs Op patients after 2000. A meta-analysis and power analysis were performed.

Results. Operative time was not significantly different between the two approaches (95% confidence interval [CI]: −0.063 to 0.992). Patient bleeding in the Lap group was significantly lower than in the Op group (95% CI: −1.027 to −0.390). Complications with Lap patients were significantly less frequent (95% CI: 0.231–0.642), and the duration of the hospital stay for Lap patients was significantly shorter (95% CI: −0.950 to −0.530) than for Op patients. Only one paper presented 80% power with 0.05 α-errors in all four outcomes, whereas four studies did not have sufficient statistical power.

Conclusions. The clinical benefits of Lap include a smaller incidence of complications and a shorter duration of hospital stay at the current time. Several studies had too few cases to sufficiently evaluate these factors, although other studies were appropriately analyzed.

Key words Laparoscopy · Liver resection · Operative time · Bleeding · Complication · Hospital stay

Introduction

Laparoscopic hepatectomy (Lap) was first reported in 1991 for the treatment of patients who have benign liver tumors in gynecologic laparoscopic surgery.[1] Since then, a pure laparoscopic approach[2–4] and hand-assisted approach[5–7] for liver resection have been developed.[8,9] Lap is ideal for patients who elect for hepatectomy because of a lower degree of invasiveness when oncological curability and perioperative safety are obtained.[9–11] However, it is difficult to guarantee both oncological safety and perioperative safety in cases with tumors located near the inferior vena cava, regardless of tumor size. Therefore, the indication for Lap is generally limited to patients in whom the tumor lies on the peripheral surface of the liver at segment (S) 3, S4, S5, or S6.[10] Conversely, recent reports have shown that even major hepatectomy can be performed using Lap.[3,12,13] Although it cannot be employed for all liver tumors, assisted-approach Lap has been widely conducted to reduce surgical stress compared to the open approach (Op).[8]

A previous meta-analysis demonstrated that operative blood loss and the duration of the hospital stay for Lap patients were significantly lower and shorter, respectively, than for Op patients.[11] Recent reports have also demonstrated that new surgical devices for liver resection might help to reduce blood loss, the duration of the hospital stay, and the total hospital fees incurred.[14] Even in our institution, the surgical devices used for liver resection in recent years are completely different from those used 10 years ago.[15] Therefore, it may be difficult to compare recent reports and older reports published more than a decade ago. The aim of the present study was to reevaluate the perioperative variables and adverse outcomes in patients undergoing Lap vs Op since 2000.

Reprint requests to: T. Mizuguchi
Received: June 21, 2009 / Accepted: March 16, 2010