国では，今日まで保険収載されたがんの分子標的薬は 16 種類に及び，薬価が 10～20 万円という高額な薬剤もある．多額の開発費，外国企業による国際価格，個別医療による薬剤の稀少化，メーカの寡占化など，高額となる多くの理由が考えられるが，新薬の審査，薬価算定の過程で経済評価をもっと重視する（データ提出の義務付けなど）ことが望まれる．

胃がんで経済分析が実施された英文の文献数は，過去 10 年間 16 件ほどで，費用効果分析は 7 件，費用効用分析は 8 件に限られる．費用効果分析では，*Helicobacter pylori* のスクリーニング効果を増分費用／効果比（incremental cost-effectiveness ratio）で分析したものが目立つ．

検診の経済的動機付け

がん対策基本法に基づくがん対策推進基本計画では，低迷するがん検診の受診率を，2011 年度以内に 50％ にする目標が設定されており，がん検診の受診率が高まれば，がん対策のエンドポイントであるがん死亡率の減少（75 歳未満の年齢調整死亡率 20％ 減少）が期待される．

検診受診者の経済的負担は大きくないとの見方もあるが，集団でなく個別に対応される人間ドックの希望者が増えていることを考えると，受診率の大幅な向上を目指すうえで，がん検診の自己負担のあり方が再検討される必要がある．また，今後，新しい検診技術の導入によっても自己負担が増加することは必定と考えられる．

多様ながん検診の自己負担額についての実態は必ずしも明らかではないので，全国のがんセンター，大学病院などのがん患者を対象に，がん検診にかかる経済的負担について自記式調査[9]を実施した（n＝2,439）．がん検診を受けたことのある者は 67.3％，検診でがんが発見された者は 32.8％ である．がんが発見された検診の内訳は，住民検診 42.6％，職場検診 21.8％，人間ドック 22.2％ である．単一の部位のがん検診の平均自己負担年額は，胃がん検診では，住民検診 2,400 円，職場検診 3,600 円，人間ドック 13,900 円である．複数部位のがん検診をみると，人間ドックでは，胃＋大腸 11,100 円，胃＋大腸＋前立腺 19,900 円，胃＋大腸＋肺 21,200 円，胃＋大腸＋肺＋前立腺

44,400 円などである．

自己負担の負担感については，検診でがんが発見された者は，住民検診・職場検診・人間ドックのいずれにおいても安いとの回答が多い．一方，高いとの回答は，がんの発見契機によらず人間ドックの費用が高いとしており，１万円を超えると負担感が増す．がん検診受診費用の税控除[10]など，がん検診受診の行動変容には，検診を受診した個人が経済的なメリットを受けられる仕組みが効果的と考えられる．

おわりに

がん医療の目覚ましい技術進歩は，確実にがん患者の福音となるが，それが高額であるために恩恵にあずかれない患者が生じるというパラドックスを内包する．分子標的薬や粒子線治療の登場は，これが相当に高額であるという意味で，従来の技術進歩への対応とは異なる仕組みが必要となっていることを先駆け的に告げているようにみえる．

今後，個別化医療，バイオ創薬，再生医療，ナノ技術，ロボット手術，遺伝子診療などの進展で，がん医療はスピーディーでダイナミックに変貌することが予感される．医療経済の観点から，こうした変化に対応しうる新たな仕組みを構築することが不可欠と考えられる．

革命的な技術も夢の新薬も，それをがん患者にあまねく届けることができなければ意味がない．がん臨床医を始め関係者が医療経済についての認識を高め，がん患者の経済的負担を最小化する工夫を行うことがますます重要となっている．その第１レベルは，臨床現場での配慮である．これには，検査・投薬・入院適用の適正化，外来治療の普及，在院日数の短縮，費用についての説明と相談などがある．

患者の経済的負担を最小化する第２のレベルは，高額療養費の現物支給の推進，ドラッグ・ラグの解消，先進医療の保険適用の迅速化など，現行制度の弾力的運用である．

第３のレベルは，がんにかかる医療制度の抜本改革である．これには，優先度に応じた資源投入（一般医療におけるトリアージ），がん患者の自己負担の軽減（３割から２～１割負担，無料化まで）があり，最も強力な対策となる．

我が国のがん患者の自己負担（直接費用のみ）の総額は，積極的治

療，フォローアップ，長期生存を合わせ，実態調査から 4,610 億円程度と推計される．また，がん検診の自己負担の総額は，5 部位の住民検診，職場検診，人間ドックを合わせて 889 億円，5 部位の受診率がそれぞれ 50 % に向上した場合は 6,094 億円と試算される．

したがって，約 1 兆円の財政措置で，現行のがん医療とがん検診の自己負担の無料化が可能になると思われる．今後のがん医療の技術進歩を考慮しても，この倍の規模，2 兆円の予算が確保できれば，技術進歩に伴う費用の増加を吸収し，相当期間にわたって，がん医療の無料化が持続できると思われる．

患者の経済的負担が重い疾病を指定して自己負担を軽減することは，現行制度でも行われており，後期高齢者医療制度のように年齢で一律に負担割合を変えるよりも合理性があると考えられる．がんは診断が明確なので，自己負担割合の軽減で医療提供側にモラルハザードが生じる恐れも少ない．

今や，男性で 2 人に 1 人，女性で 3 人に 1 人の死因となるがんは，国民の最も身近な病気であり，死の恐怖とも絡んで不安の大きい病気である．したがって，がん医療の無料化は，老後の確かな安全保障とも言えるものである．フランスは，軽度な病気の治療に用いる薬剤の自己負担割合を高くする一方，がん医療の無料化は 21 世紀になる前から実現させている．

濃沼信夫

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III 大腸癌治療の費用効果

1. 大腸癌診療で知っておきたい医療経済

Cancer economics in the treatment of colorectal cancer

濃沼　信夫

ポイント

- 大腸癌の医療費は3,671億円，癌医療費の14.3%を占めると推計される．
- 大腸癌のcost of cancerは，医療費に，morbidity cost 760億円，mortality cost 7,948億円を加えた1兆2,379億円と算定される．
- 大腸癌患者の年間の自己負担額は平均97.4万円，償還・給付額は70.6万円である．
- 大腸癌検診の受診率向上は喫緊の課題であるが，二次予防で医療費削減効果を得るには精度の向上（発見率の向上，発見の早期化）と業務の効率化が不可欠である．
- 大腸癌の手術後フォローアップは，Stage Ⅱ・Ⅲについては経済的効果が高い．

I. 大腸癌の医療費

国民医療費33兆1,289億円のうち，悪性新生物の医療費は2兆5,748億円で，7.8%を占める（平成7年国民医療費）．部位別の医療費は公表されていないので，人口動態調査，社会医療診療行為別調査，患者調査を用いて推計すると，大腸癌は3,671億円である．

大腸癌の医療費は，癌医療費の14.3%（結腸8.7%，直腸5.6%）を占めてもっとも多く，次いで胃12.4%，肺11.8%などの順である．男性（1兆4,195億円）では，大腸は14.2%で，胃14.5%，肺14.5%と並んで多い．女性（1兆1,553億円）では，大腸は14.3%で，乳房17.7%に次いで多い．

癌による社会経済的な損失は，国民医療費に計上される直接医療費だけではないはずである．直接医療費に間接医療費を加えた，cost of cancerを試算すると，年間9兆6,822億円となり，GDPの2%に匹敵する巨額に上る[1]．

間接費用には，入院や通院による労働生産性の低下（morbidity cost）各4,182億円，1,275億円と，早期死亡による逸失利益（mortality cost）6兆5,617億円がある．精神的な費用[2]を間接費用に計上することもあるが，算定が容易でないので，ここでは加えていない．

大腸癌のcost of cancerは，医療費3,671億円，入院のmorbidity cost 576億円，通院

のmorbidity cost 184億円，mortality cost 7,948億円を合わせた1兆2,379億円と推計される．

cost of cancerに占めるmortality costの割合は，全部位で67.8％であり，部位別では，肺76.2％，胃71.7％，大腸64.2％，乳房55.9％などである．この割合は，罹患率と死亡率との比(mortality-to-incidence rate ratio)，二次予防の効果，治療成績の向上などが影響すると考えられ，cost of cancerからも癌医療の評価ができる．癌医療の第一義的なエンドポイントが救命にあるとすれば，mortality costを減らすことはきわめて重要といえる．

cost of cancerは，癌医療の経済評価に用いられるとともに，癌予防と癌医療の意義について国民の理解と意識を高めるのに役立つ．また，効果的，効率的な政策決定と資源配分を促し，癌医療に必要な財源を確保するうえでも有用である．たとえば，「交通事故による経済的損失は3兆2,672億円で，国民1人当りに換算すると年間約22,000円(2007年度)」[3]として，交通事故対策を進めることの重要性を国民や財政当局にアピールするように，癌対策を強力に推進するうえで，cost of cancerの概念は広く活用される必要があろう．

Ⅱ．患者の経済的負担

わが国は国民皆保険による現物支給(1～3割の患者負担)や高額療養費(自己負担限度額)により，患者の経済的な負担は最小限で済むことになっている．しかし，長足の技術進歩に伴う高額な薬剤や機器の登場，自己負担率の引き上げなどにより，患者の経済的負担は増大する傾向にある．最近の世論調査では，「深刻な病気にかかったときに医療費を払えない」との不安を感じる国民の割合は8割を超えている[4]．

1．患者負担の実態

癌の診療における患者の経済的負担については，これまで十分なデータがなかった．たとえば，レセプト(診療報酬明細書)を用いての患者自己負担の推計には限界があった．レセプトは施設別なので，連携で複数の施設で受療した場合は連結が困難だからである．

そこで，患者自身に領収証や家計簿を見ながら，負担額を記入してもらう調査を行ったところ，治療中の癌患者の平均自己負担額は，年間100.7万円に上っていた(n = 6,604，平均年齢63.3歳，高額な粒子線治療の患者は除く)[5]．直接費用は，入院費用51.9万円(該当患者74.4％)，外来費用18.1万円(同100％)，交通費4.5万円(同93.7％)である．また，間接費用は，健康食品・民間療法21.7万円(同56.8％)，民間保険料25.3万円(同85.1％)，その他13.8万円(同42.5％)である．

一方，償還ないし給付される金額は，平均62.5万円である．内訳は，高額療養費28.3万円(該当患者52.6％)，税の医療費還付8.6万円(同23.2％)，民間保険給付101.8万円である．したがって，実質の平均自己負担額は38.2万円と考えられる．

大腸癌患者(n = 433)についてみると，平均自己負担額は97.4万円，償還・給付額は70.6万円で，実質の平均自己負担額は，26.8万円となる(**図1**)[5]．

一般に化学療法，放射線療法を実施した場合は，自己負担が増加する傾向にあり，医学的理由ではなく，経済的理由で治療の中止・変更を余儀なくされる患者が出てきている．癌の臨床医691名に調査を実施し，経済的理由で治療の中止・変更を行った患者の割合を推計したところ，入院で0.83％，外来で0.05

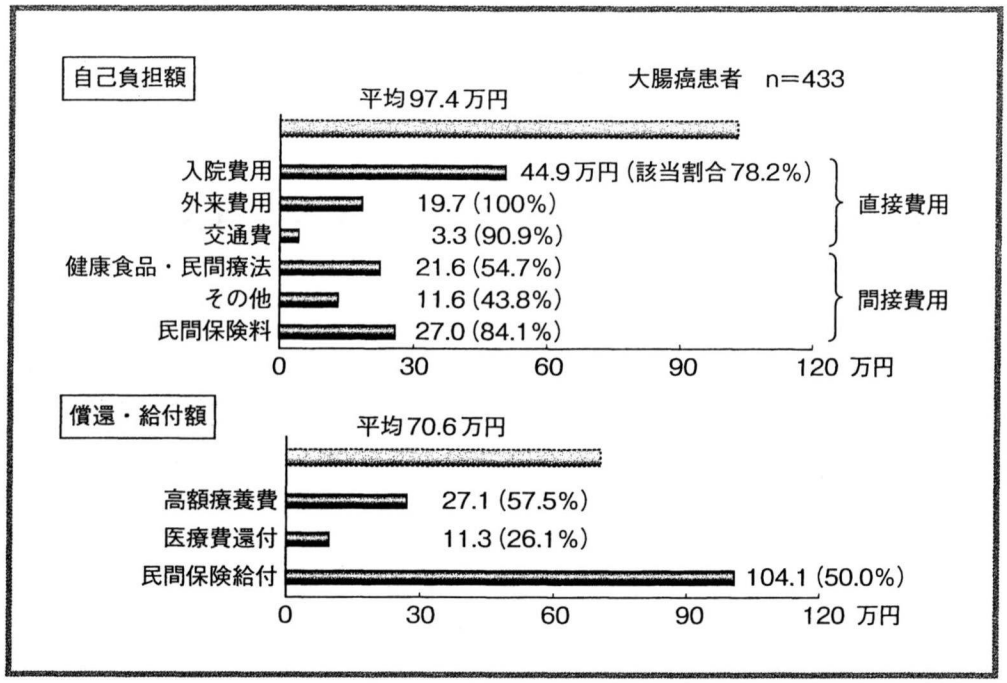

図1　大腸癌患者の自己負担額と償還・給付額（年間）[5]

%であった[6]．

癌患者の経済的な負担感をVAS（ビジュアル・アナログ尺度）で調査すると，「非常に重い」から，「負担感はまったくない」まで，分散が大きい．経済的負担感を構成する要因に関する階層的重回帰分析を行うと，窓口での外来費用や交通費によって負担感の増すことがわかる[5]．年収や貯蓄の多寡も負担感の大きな要因と考えられる．QOL（EQ-5D）との関連をみると，不安，ふさぎ込み，家族に迷惑をかけていると思う場合などでも負担感が増すことが判明した．

2. 患者負担の最小化

「がん対策基本法」には，患者に等しく適切な癌医療を提供することが謳われ，患者の経済的な悩みにも十分な対応することが求められている．癌医療の進歩をあまねく患者に届け，患者中心の癌医療を展開するには，質，効率，安全の確保とともに，患者の自己負担を最小限にする工夫が必要となっている．

このためには，第一に，検査や投薬，入院適用の適正化，在院日数の短縮，ジェネリック医薬品の使用，コスト情報を含むインフォームド・コンセントの確保など，臨床現場で患者の経済的負担を軽減する配慮が重要となっている．第2に，高額療養費の現物給付化（2007年導入）の普及，先進医療の保険導入の推進，新薬などの保険適用の迅速化など，現行制度の弾力的運用が必要といえる．第3に，癌患者の自己負担割合の軽減，高額療養費の限度額引き下げなど，医療保険制度の見直しが検討される必要がある．

米国オレゴンヘルスプランのように優先度の高い医療により多くの財源を投入する[7]ことや，フランスのように癌治療の費用を全額償還する[8]などの施策が，日本にとっても参考になりうる．癌患者の自己負担額（直接費用）の総額は4,610億円程度と推計され，5,000億円規模の財政出動があれば，癌患者の経済的負担を大幅に軽減することができると思われる．

Ⅲ. 癌検診の医療費節減効果

1. 検診受診率は2割

大腸癌検診の受診率は，老人保健事業報告（平成19年度）で18.8%，国民生活基礎調査（同）で男性27.5%，女性22.7%と，20%前後に低迷している．がん対策基本法に基づく「がん対策推進基本計画」では，5年以内に癌検診の受診率を50%にする目標が設定されており，その目標年は2年半後に迫っている．

便潜血検査（FOBT）による大腸癌検診は，欧米（化学法）の無作為比較対照試験（RTC），および，わが国（免疫法）の症例対照研究で死亡率減少効果が認められており[9]，わが国では対策型検診として，平成4年から老人保健事業に組み込まれている．ただし，目標年までの限られた期間に，現行の数倍の検診受診率を実現することは厳しい状況といえる．

大腸癌の生存率は，OECDの医療の質プロジェクト（HCQI）が選定した，国際的に医療の質を評価する13の指標の一つであり[10]，検診受診率の改善は大腸癌対策にとってきわめて重要な課題である．

2. 受診率向上の医療費節減効果

一方，受診率が現行の数倍に向上した場合の，検診の応需体制の整備（人材，財源）とともに，癌医療費の節減効果の見通しを明らかにしておく必要がある．

そこで，検診受診率が現行の1.5～3倍に向上し，早期発見，早期治療を行う患者が増加することで節減できる癌医療費を，Markovモデル（検診費用を含む癌の生涯医療費と賃金稼得額のバランスシート）を用いて算出した[11]．検診受診率の向上に伴い，検診コストの削減，発見率の向上，発見Stageの早期化が見込まれるので，これら独立した3要素の8通りの組み合せで，癌医療費の増分を性別，年齢階級別に推計した．

すなわち，大腸癌の検診受診率18.6%（平成18年度老人保健事業報告）が1.5倍（27.9%）から3倍（55.8%）にまで向上した場合の，癌医療費の変化をシミュレーションした．上記3要素が現状のままの場合，男性（費用便益比3.10）では，1.5倍で13億円，3倍では50億円の医療費増加となる（表）．女性（費用便益比1.20）では，同じく34億円，135億円の医療費増加となる．

一方，検診受診率の向上と同じ割合だけコストの削減，発見率の向上，発見の早期化が実現した場合には，受診率1.5倍では男性で48億円，女性で27億円，3倍では各346億円，185億円の医療費の節減効果が期待できる．これら三つの要素は独立して医療費の節減に関わるが，たとえば，男性の結腸癌では発見率の向上が，女性の結腸癌ではコストの削減が，医療費の節減にもっとも寄与することがわかる．

医療経済の観点からは，検診受診率の向上に併せて精度の向上（発見率の向上，発見の早期化）と業務の効率化（コストの削減）をはかることがきわめて重要といえる．

Ⅳ. 術後フォローアップの経済的意義

最近の癌治療は，初期治療に加えて長期フォローアップの重要性が増している．技術進歩などで長期生存者が増加し，失われた機能の回復や再発の防止が大きな課題になってきたためである．しかし，フォローアップの方法や有効性について，経済面からの検討はほとんどなされていない．そこで，大腸癌の手術後フォローアップに係る資源投入の妥当性などを判定するシステムモデルを開発した．

すなわち，大腸癌の術後ファローアップの経過を類型化し，再発形式，生存予後，患者

表 検診受診率向上による結腸癌医療費の増減（男性）

＜大腸癌検診受診率：現行 18.6%＞　　＜老人保健法による検診（単位：億円）＞

受診率向上につれ			受診率向上による差益（費用便益分析）			
コスト	発見率	発見時 Stage	1.5倍	2.0倍	2.5倍	3.0倍
現行のまま	現行のまま	現行のまま	－13億円	－25億円	－38億円	－50億円
削減	現行のまま	現行のまま	15	30	45	61
現行のまま	向上	現行のまま	10	36	76	132
現行のまま	現行のまま	早期化	－6	－10	－13	－16
削減	向上	現行のまま	38	91	159	242
削減	現行のまま	早期化	22	46	70	95
現行のまま	向上	早期化	20	66	137	235
削減	向上	早期化	48	121	220	346

〔平成18年度地域保健・老人保健事業報告，システムモデルより作成〕

QOL，医療費を比較するシステムモデルを開発し，費用便益分析を実施した．算出には簡易生命表，診療報酬点数表，総務省日本統計年鑑のデータを用い，モデルに投入するパラメータは，大腸癌術後フォローアップ研究会（杉原健一代表）の登録症例（全国16施設*，5,599例，観察期間5年）を用いた．

Stage Ⅰの大腸癌1,599例（結腸814例，直腸785例）をみると，再発率は各2.5%，7.3%，再発後生存率は各15.0%，33.3%である．術後フォローアップに要する総費用は各2億3,383万円，2億6,843万円，生存者の労働生産性（賃金稼得額）は各3,266万円，1億2,333万円であり，費用便益比は各0.14，0.46となる（費用＞便益，**図2**）．したがって，Stage Ⅰは，現時点ではフォローアップの経済的な効果は少ないといえる[12]．

生存率の増減と生存期間の増減との関係から，フォローアップが実施されない場合は生存率が10%低下（生存期間が20%短縮）するとして，Stage Ⅰでは，フォローアップ費用に対する生産性の増分は，結腸－29.5%，直腸－80.3%となる．また，フォローアップの精度向上で生存率が5%向上（生存期間が10%延長）すると，これは各6.9%，17.2%となる．Stage Ⅰでは，ファローアップ費用の低減と，再発後生存率の改善が重要と考えられる．

一方，Stage Ⅱ 2,060例（結腸1,270例，直腸790例）をみると，再発率は各13.4%，22.8%，再発後生存率は各27.6%，19.4%で，費用便益比は各0.86，1.34となる．フォローアップで生存率が5%向上すると，フォローアップ総費用に対する生産性の増分は，各28.2%，35.3%となる．

また，Stage Ⅲ 1,940例（結腸1,008例，直腸932例）をみると，再発率は各25.0%，39.6%，再発後生存率は各22.6%，17.3%で，

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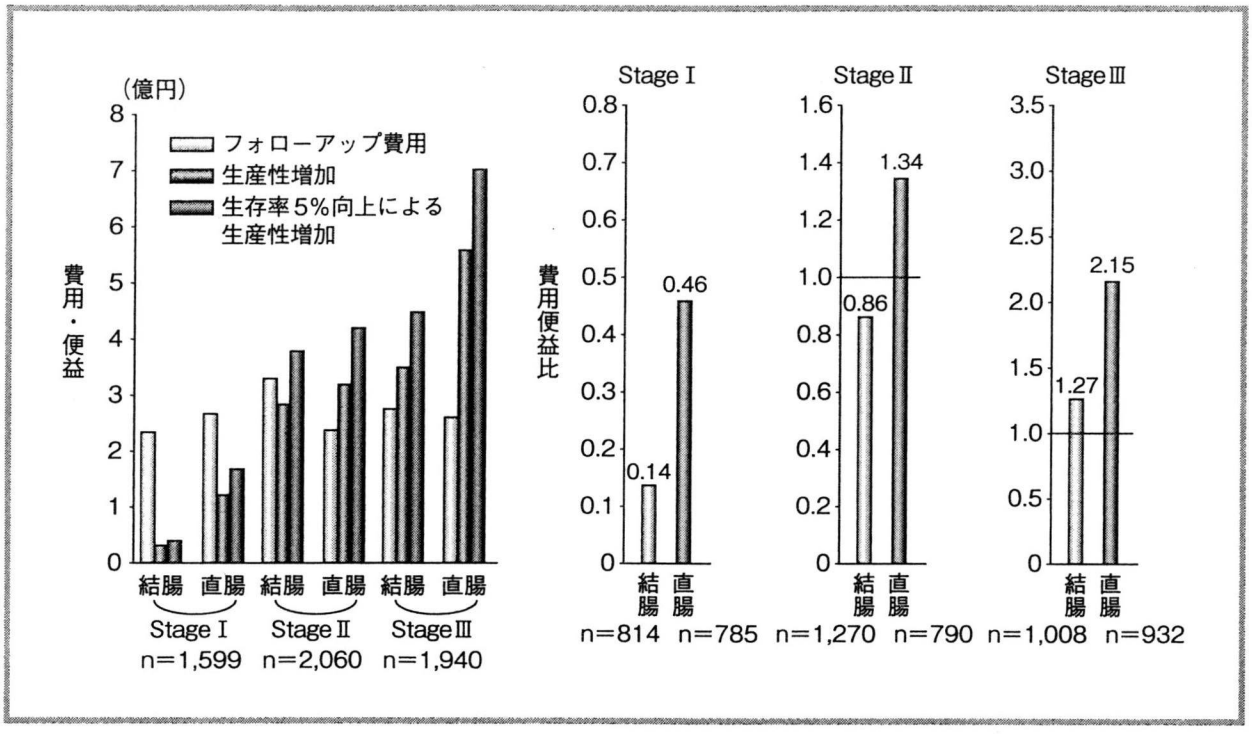

図2　部位別，Stage別にみた大腸癌術後フォローアップの費用，便益，費用便益比
〔科学研究費補助金「がん手術後フォローアップに対する医療経済評価ツールの開発に関する研究」2005-2007〕

費用便益比は各1.27，2.15（費用＜便益）となる．Stage Ⅱ・Ⅲの大腸癌はフォローアップの経済効果が示唆され，再発後生存率の向上によりさらなる費用便益比の増大が期待できると考えられる．

再発を1人発見するのに要する費用は，Stage Ⅰでは結腸1,169万円，直腸471万円，Stage Ⅱでは各195万円，132万円，Stage Ⅲでは各110万円，70万円である．また，1人救命に要する費用は，Stage Ⅰでは各7,794万円，1,413万円，Stage Ⅱでは各704万円，679万円，Stage Ⅲでは各484万円，406万円である．Stage Ⅱ・Ⅲについては，これらは社会的に支出を容認しうる水準と考えられる．

大腸癌の手術後フォローアップの意義について医療経済の観点から検討したところ，上記のとおり，Stage Ⅰについては再発後生存率の改善が課題であること，Stage ⅡおよびⅢについては経済的効果が高いことが判明した．

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ORIGINAL ARTICLE

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Analysis of stage IVB endometrial carcinoma patients with distant metastasis: a review of prognoses in 55 patients

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Abstract
Background. Adequate treatment for extremely advanced endometrial cancer is unknown. The purpose of this study was to clarify the prognosis of patients with stage IVB endometrial carcinoma and the validity of treatment. Furthermore, we evaluated whether there was a connection between the prognosis and the site of metastasis.
Methods. The prognoses of 55 patients with stage IVB endometrial carcinoma were studied with reference to the initial treatment method and the metastatic site at the time of the initial treatment.
Results. The median survivals of the group of 35 patients who were initially treated with surgery and the group of 10 patients who underwent radiotherapy or chemotherapy as their initial treatment followed by surgery were 11.5 months and 9.5 months, respectively. The residual tumor diameter after surgery was precisely measured in 40 of these 45 patients. The prognosis was significantly better in the patients with a residual tumor diameter of less than 2 cm compared to those with a tumor diameter of 2 cm or greater, and the median survival periods in these two groups were 23.5 months and 11.5 months, respectively (P = 0.027). Furthermore, the prognosis of patients with lung metastasis was significantly better than that of patients with non-lung hematogenous metastasis; the median survival periods of these two groups were 18.5 months and 10.5 months, respectively (P = 0.014).
Conclusion. For operable patients, surgery as an initial treatment and reduction of the residual tumor size to less than 2 cm appeared to contribute to a better prognosis. In addition, conservative initial treatment and the presence of non-lung hematogenous metastasis were poor prognostic factors.

Key words Endometrial carcinoma · Stage IVB · Operation · Preoperative therapy · Cytoreductive surgery · Metastasis

Introduction

Endometrial carcinoma is the most frequent gynecological malignant tumor in the United States,[1] and recently it has tended to occur with increasing frequency in Japan. A majority of patients with endometrial carcinoma are treated when the cancer is at an early stage;[2] however, the frequency of stage IV endometrial carcinoma with distant metastasis is reported to be 3%–13%,[2–5] with a 5-year survival rate of 10%–20%.[3,5] Stage IVB endometrial carcinoma has a poor prognosis, but it has been reported that, after reducing the tumor mass with initial surgery, adjuvant therapy can be performed effectively and the overall survival (OS) can be prolonged.[6–8] On the other hand, there are occasions where preoperative chemotherapy or radiotherapy is performed prior to a decision to perform surgery; for example, in patients with ovarian cancer, or in patients with stage IVB endometrial carcinoma if surgery is not suitable as an initial treatment considering the general condition of the patient and the status of tumor spread. A detailed evaluation of the prognosis in such patients has not been reported. One of the purposes of this study was to clarify the prognosis of patients with stage IVB endometrial carcinoma and to determine the significance of surgery, preoperative chemotherapy, and radiotherapy for their prognoses. We also evaluated whether

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there was a connection between the prognosis and the site of metastasis in these patients.

Patients and methods

During the 22 years from January 1985 to December 2006, 877 patients with endometrial carcinoma were treated at the Kanagawa Cancer Center. Among these patients, there were 55 patients (6.3%) with stage IVB endometrial carcinoma according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) staging classification. These patients were studied retrospectively. Patients who had undergone surgery, chemotherapy, or radiotherapy previously as an initial treatment were included. In addition, patients receiving only best supportive care were also included. Endometrial cancer patients with concurrent cancers were excluded. The diagnosis of lymph node metastasis, including paraaortic lymph nodes, was determined as significant lymph node enlargement of more than 1.5 cm shown on computed tomography (CT) scans or magnetic resonance imaging (MRI). From 2003, if the diagnosis of distant metastases was difficult to make by CT or MRI, fluorodeoxyglucose positron emission tomography (FDG-PET) was used to make the definitive diagnosis.

Among the criteria used to determine each treatment procedure, surgery, including hysterectomy with bilateral salpingo-oophorectomy, was the first choice to control the local primary disease and to evaluate the tumor spread in the intraperitoneal cavity, as long as the patient's general condition was good enough to tolerate the operation. In patients whose performance status (PS) was too poor for surgery, radiation therapy was chosen as the initial treatment, if stopping external bleeding was crucial. Chemotherapy was performed as an initial treatment in patients with poor PS but tolerable external bleeding, with the aim of reducing both primary and metastatic lesions.

When the Gynecologic Oncology Group (GOG) PS was good (0–2) and at least hysterectomy was assumed to be possible as an initial treatment, a simple total hysterectomy with bilateral salpingo-oophorectomy was performed as the standard operation. When there was no gross residual tumor in the peritoneal cavity, retroperitoneal lymph node dissection was also performed. If massive multiple metastases were found before any initial treatment or if the PS was too poor for surgery (PS 3–4) or if serious general complications were present, chemotherapy or radiotherapy was initiated. For the chemotherapy, the CAP regimen (cisplatin 50 mg/m^2; cyclophosphamide 500 mg/m^2; pirarubicin 30 mg/m^2) was administered to patients from 1985 to 1998, and the TC regimen (paclitaxel 175 mg/m^2; carboplatin AUC = 5.0) was administered to patients from 1998 to 2006. For the radiotherapy, total pelvic irradiation of 48–60 Gy was applied.

The prognosis was examined with regard to the patient's age, histological type, initial treatment method, residual tumor diameter after surgery, and metastatic sites at the initiation of treatment. To assess the prognosis, overall survival (OS) was analyzed for all patients. The survival rate was calculated by using all causes of death and the cumulative survival rate was estimated by the Kaplan-Meier method.[9] OS was assessed by the bilateral log-rank method.[10] For survival analysis, event time distributions were estimated using the method of Kaplan and Meier, and differences in survival rates were compared using the log-rank test and the Cox proportional hazards regression model.[11] Statistically significant differences were defined as $P < 0.05$ for all tests. And finally, χ^2 analysis was used to identify variables.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 60 years (range, 31–81 years); 7 patients (12.7%) were premenopausal and 48 patients (87.3%) were postmenopausal. The most frequent histological type was endometrioid adenocarcinoma, in 29 patients (52.7%); the others were: 7 patients (12.7%) with serous adenocarcinoma; 5 patients (9.1%) with adenosquamous cell carcinoma; 5 patients (9.1%) with carcinosarcoma; 4 patients (7.3%) with adenoacanthoma; 3 patients (5.5%) with small cell carcinoma; 1 patient (1.8%) with clear cell adenocarcinoma; and 1 patient (1.8%) with undifferentiated carcinoma. The GOG PS was 0–2 in 51 patients (92.7%) and 3–4 in 4 patients (7.3%).

Metastatic sites

Distant metastasis patterns in the stage IVB endometrial carcinoma patients at the time of initial treatment were classified into three groups: hematogenous metastasis; intraperitoneal metastasis; and distant lymph node metastasis, according to the main routes through which endometrial cancer cells spread (Table 2). Hematogenous metastasis

Table 1. Patient characteristics

Number of patients	55
Age (years)	
Median	60
Range	31–81
Menopause	No. of patients (%)
Premenopausal	7 (12.7)
Postmenopausal	48 (87.3)
Cell type	No. of patients (%)
Endometrioid adenocarcinoma	29 (52.7)
Serous adenocarcinoma	7 (12.7)
Adenosquamous	5 (9.1)
Carcinosarcoma	5 (9.1)
Adenoacanthoma	4 (7.3)
Small cell carcinoma	3 (5.5)
Undifferentiated	1 (1.8)
Clear cell adenocarcinoma	1 (1.8)
GOG performance status	No. of patients (%)
0–2	51 (92.7)
3–4	4 (7.3)

GOG, Gynecological Oncology Group

Table 2. Metastatic sites

Classification of metastatic sites	No. of patients (%)
Hematogenous metastasis[a]	24 (43.6)
Lung	16 (29.1)
Bone	7 (12.7)
Liver	4 (7.3)
Brain	1 (1.8)
Intraperitoneal metastasis	36 (65.5)
Peritoneum	22 (40.0)
Omentum	14 (25.5)
Distant lymph node metastasis	8 (14.5)
Supraclavicular lymph node	6 (10.9)
Inguinal lymph node	2 (3.6)

[a] Some patients had metastases at more than one site

Table 3. Methods of treatment

Classification	No. of patients (%)
Operation as initial treatment	35 (63.6)
Adjuvant therapy after operation	30
Chemotherapy only	26
Radiation only	1
Chemotherapy and radiation	3
Neoadjuvant therapy before operation	10 (18.2)
Chemotherapy	8
Radiation	2
Chemotherapy only	7 (12.7)
No treatment	3 (5.5)

was seen in 24 patients (43.6%), among whom there were 16 patients (29.1%) with lung metastasis, 7 patients (12.7%) with bone metastasis, 4 patients (7.3%) with liver metastasis, and 1 patient (1.8%) with brain metastasis. Intraperitoneal metastasis was seen in 36 patients (65.5%), among whom there were 22 patients (40.0%) with peritoneal dissemination and 14 patients (25.5%) with omental metastasis. Distant lymph node metastasis was seen in 8 patients (14.5%), among whom there were 6 patients (10.9%) with supraclavicular lymph node metastasis and 2 patients (3.6%) with inguinal lymph node metastasis.

Methods of treatment

The classification of the treatment methods is shown in Table 3. Thirty-five patients (63.6%) underwent initial surgical treatment and the PS was 0 in all patients. Among them, postoperative adjuvant therapy was performed in 30 patients: radiotherapy was performed in 1 patient (total pelvic irradiation 60 Gy); chemotherapy alone was performed in 26 patients (CAP regimen in 13 patients, TC regimen in 13 patients); and combined chemotherapy and radiotherapy were performed in 3 patients (CAP regimen and total pelvic irradiation in 3 patients). In 5 patients, adjuvant therapy was not performed, taking the general condition of the patients into consideration.

In 20 patients (36.4%), surgery could not be selected as an initial treatment. Among them, 17 patients (30.9%) were treated initially with chemotherapy (CAP in 10 patients, TC in 5 patients) or radiotherapy (2 patients), and 10 patients could then undergo surgery (PS 0–1). Of these 10 operable patients, 8 patients had preoperative chemotherapy and 2 patients had preoperative radiotherapy. All 7 patients who could not undergo surgery because of general complications or poor PS had only chemotherapy. Three patients who were untreated and whose condition deteriorated had a PS score of 3.

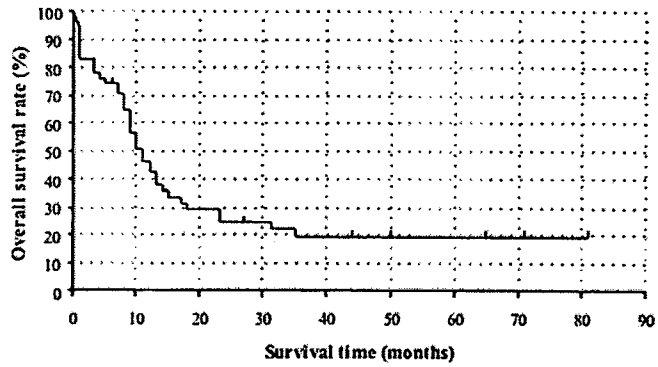

Fig. 1. Overall survival rate of all 55 patients with stage IVB endometrial carcinoma

Survival analysis

The OS rate of all patients with stage IVB endometrial carcinoma is shown in Fig. 1. The median survival period was 10.5 months (range, 0–81 months; mean survival period. 16.9 months), and the 5-year survival rate was 20.2%. During the observation period, 14 of the 55 patients survived, 41 patients died, and 9 patients showed no recurrence.

A summary of the median survival periods of patients stratified into subgroups with regard to age, histological type, metastatic site, initial treatment, and residual tumor diameter is shown in Table 4. For age, survival was analyzed after dividing the patients into two groups: those aged 60 years (which was the median age) or younger, and those 61 years or older. However, there was no significant difference between these groups. For the histological type, the patients were also divided into two groups: endometrioid adenocarcinoma G1 plus G2, and all other histological types. The median survival periods for these two groups were 15.5 months and 10.5 months, respectively. The endometrioid adenocarcinoma G1, G2 group showed better survival than the other group, but there was no statistically significant difference between the two groups.

The OS of the 35 patients with surgery as the initial treatment and the OS of the 10 patients who underwent surgery after radiotherapy or chemotherapy as an initial treatment are shown in Fig. 2. The median survival periods of these groups were 11.5 months (range, 0–81 months; mean survival, 18.6 months) and 9.5 months (range, 1–44 months; mean survival, 14.5 months), respectively. The group that had surgery as the initial treatment showed a better prognosis than the group that received preoperative therapy; however, there was no significant difference between these groups ($P = 0.302$). The 5-year survival rate was 25.4% in

Table 4. Survival analysis

Variables	Number of patients (%)	Median survival period (months)
Age (years; $n = 55$)		
31–60	31 (56.4)	10.5
61–81	24 (43.6)	15.5
Histology ($n = 55$)		
Endometrioid G1 G2	14 (25.5)	15.5
All others	41 (74.5)	10.5
Initial treatment ($n = 55$)		
Surgery	35 (63.6)	11.5
Chemotherapy or radiotherapy followed by surgery	10 (18.2)	9.5
Chemotherapy only/no treatment	10	ND
Residual tumor diameter ($n = 40$)		
Less than 2 cm	18 (45.0)	23.5
2 cm or more	22 (55.0)	11.5
Metastatic sites ($n = 55$)		
Hematogenous metastasis	24 (43.6)	11.5
Lung	16 (29.1)	18.5
All sites other than lung	8 (14.5)	10.5
Intraperitoneal metastasis	36 (65.5)	12.5
Distant lymph node metastasis	8 (14.5)	12.5

ND, not determined

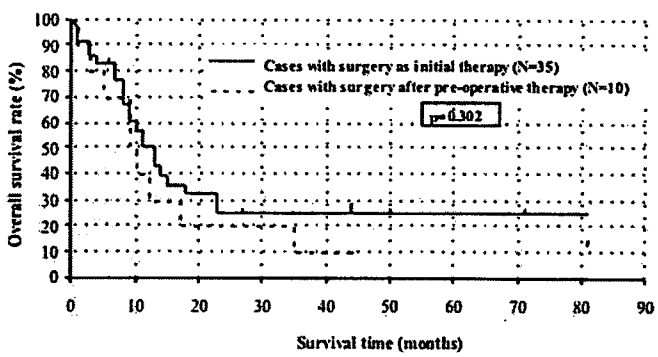

Fig. 2. Overall survival rates of the 35 patients who underwent surgery as the initial treatment and the 10 patients who underwent surgery after radiotherapy or chemotherapy as the initial treatment

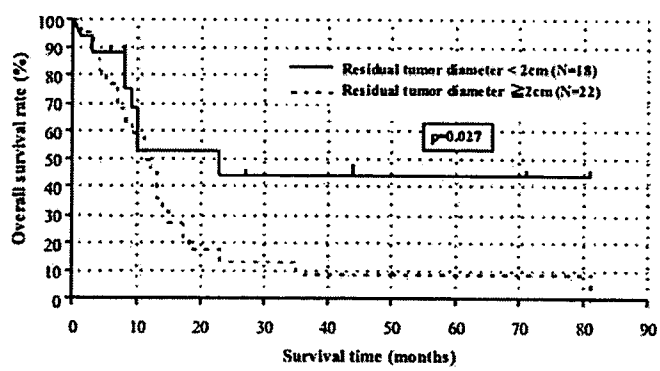

Fig. 3. Overall survival rates of the 22 patients with a residual tumor diameter of 2 cm or more and the 18 patients with a residual tumor diameter less than 2 cm

the group with surgery as the initial treatment and 14.1% in the group with radiotherapy or chemotherapy as the initial treatment, regardless of whether or not there was any subsequent surgical treatment ($P = 0.542$).

In 40 of the 45 patients who underwent surgery, there was a clear description of the residual tumor diameter. The prognoses were analyzed in the patients with a residual tumor diameter of 2 cm or more and in those with a tumor diameter of less than 2 cm (Fig. 3). The median survival periods in these two groups were 11.5 months (range, 1–81 months; mean survival, 16.3 months) and 23.5 months (range, 0–81 months; mean survival, 20.6 months), respectively. The OS showed that patients with a residual tumor diameter of less than 2 cm had a significantly better prognosis than those with larger tumor diameters ($P = 0.027$).

The OS rates of the groups with hematogenous distant metastasis, intraperitoneal disseminated metastasis, and distant lymph node metastasis are shown in Fig. 4. The median survival periods in these three groups were 11.5 months (range, 0–81 months; mean survival, 18.5 months),

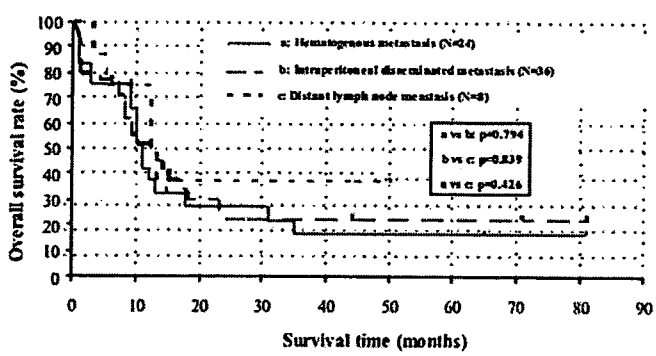

Fig. 4. Overall survival rates of the 24 patients with hematogenous distant metastasis, the 36 patients with intraperitoneal disseminated metastasis, and the 8 patients with distant lymph node metastasis

12.5 months (range, 0–81 months; mean survival, 15.8 months), and 12.5 months (range, 3–50 months; mean survival, 19.3 months), respectively. There were no significant differences between the groups. When the hematogenous

Table 5. Multivariate analysis using prognostic factors

	Risk ratio	95% CI	*P* value
Initial treatment other than surgery	3.28	1.253–8.586	0.016
Lung metastasis[a]	0.27	0.074–0.965	0.044
Hematogenous metastasis	2.16	0.492–9.449	NS
Intraperitoneal disseminated metastasis	1.13	0.274–4.661	NS
Distant lymph node metastasis	0.34	0.102–1.136	NS
Diameter of residual tumor 2 cm or more	2.76	1.126–6.750	0.026

[a] Lung metastasis without other hematogenous metastatic lesions
CI, confidence interval; NS, not significant

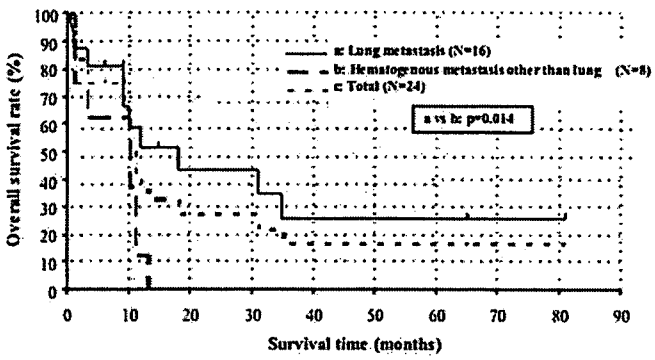

Fig. 5. Overall survival rates of the 16 patients with lung metastasis and the 8 patients with non-lung hematogenous metastasis

metastasis group was divided into a lung metastasis group and a non-lung metastasis group, these groups' median survivals were 18.5 months (range, 0–81 months; mean survival, 24.1 months) and 10.5 months (range, 1–13 months; mean survival, 7.5 months), respectively. The OS showed that the non-lung hematogenous metastasis group had a significantly poorer prognosis ($P = 0.014$; Fig. 5). The 5-year survival rates were 26.4% in the lung metastasis group, 0% in the non-lung hematogenous metastasis group, 23.7% in the intraperitoneal disseminated metastasis group, and 34.0% in the distant lymph node metastasis group.

Multivariate analyses using each prognostic factor examined (Table 5) showed that conservative management with chemotherapy or irradiation as the first treatment and a residual tumor diameter of more than 2 cm after the operation were significant poor prognostic factors (risk ratios 3.28 and 2.76, respectively). Lung metastasis without other hematogenous metastasis was a significant factor for better prognosis (risk ratio 0.27).

The clinical courses in 17 of the 20 patients who could not undergo initial surgical treatment, because of poor PS and/or a massive tumor spread, were as follows. Two patients with inguinal lymph node metastasis were treated with irradiation of both inguinal lymph nodes and pelvis as the first treatment, followed by total abdominal hysterectomy (TAH) and bilateral oophorectomy (BSO). Both patients had residual tumors that were more than 2 cm in diameter and they died because of progression of peritoneal dissemination. Fifteen patients had chemotherapy as the first treatment; CAP was used in 10 patients and TC in 5 patients.

Of these 17 patients, 2 patients with lung metastasis without other hematogenous metastasis have survived with complete remission. One had CAP followed by TAH and BSO (suboptimal operation), and the other had TC followed by radiation therapy.

Discussion

The prognosis of stage IVB endometrial carcinoma is poor, with a 10%–20% 5-year survival rate.[3–5] This is partly because the response rates to radiotherapy, chemotherapy, and hormone therapy for large residual tumors are low. It has been reported that aggressive cytoreductive surgery in patients with stage IVB endometrial carcinoma improves the prognosis. However, when patients at our hospital were reviewed, 36.4% of the stage IVB patients were inoperable. In the present study, we evaluated patients to see if the prognosis was influenced by when surgery was performed as an initial treatment approach or by the choice of preoperative chemotherapy, radiotherapy, or both. In addition, as background evaluation for these patients, we investigated whether differences in metastatic sites influenced the prognosis.

Goff et al.[6] reported that 29 of 47 patients with stage IV endometrial carcinoma could undergo surgery without leaving a bulky tumor and that the median survival period was 19 months, while the median survival period of 18 patients who did not undergo surgery was 8 months. Chi et al.[7] reported that in 55 stage IV endometrial carcinoma patients who underwent surgery as an initial treatment, the median survival period of patients with a residual tumor diameter of less than 2 cm was 31 months, while the median survival period of patients with a residual tumor diameter of more than 2 cm was 12 months and that of the inoperable patients was 3 months. Bristow et al.[8] reported that in 65 stage IVB endometrial carcinoma patients who underwent surgery as an initial treatment, the median survival period of patients with a residual tumor diameter of less than 1 cm was 34.3 months, while the median survival period of patients with a residual tumor diameter of more than 1 cm was 11.0 months. In our study, the survival period was also significantly prolonged in the patients with a residual tumor diameter of less than 2 cm.

Our study showed that the patients who received initial surgical treatment tended to have a better prognosis than the patients who received preoperative chemotherapy or

radiotherapy followed by surgery. Reports of preoperative chemotherapy in endometrial carcinoma are rare.[12] Our study failed to show a positive effect of preoperative chemotherapy or radiotherapy. In the patients with chemotherapy and/or radiotherapy as an initial treatment, the treatment response was very low, and only half of these patients could undergo subsequent surgery. Furthermore, of the patients that could undergo surgery, 50% were unable to undergo optimal surgery. Campagnutta et al.[13] studied 9 patients with recurrent endometrial carcinoma who had received preoperative chemotherapy at the time of recurrence, and reported that there was no improvement in either the surgery completion rate or the survival rate.

In Western countries, preoperative radiotherapy is performed more frequently than in Japan. Especially in patients in whom the cervix is enlarged by invasion, it has been reported that combined preoperative radiotherapy and surgery is useful.[14,15] Also, National Comprehensive Cancer Network (NCCN) guidelines[16] recommend radiotherapy or a radiotherapy-surgery combination according to circumstances in patients with extrauterine extension, such as invasion to the vagina, bladder, rectum, or parametrium. Landgren et al.[17] reported that the 5-year survival rate was 26% in 26 patients with unresectable advanced endometrial carcinoma treated with irradiation. In Japan, unlike Western countries, preoperative chemotherapy is often used in the treatment of endometrial carcinoma, especially for patients with distant metastasis. We have patients in whom uterine perforation developed after radiotherapy. Therefore, the value of chemotherapy in the initial treatment of advanced endometrial cancer patients should be re-evaluated and the effectiveness of the recent extensive use of multidrug combination therapy including paclitaxel/docetaxel should be clarified.

In some reports, age is considered to be an important factor related to the prognosis.[7,18,19] On the other hand, it has also been reported that this relationship was not observed.[8] Our study results also did not show age to be clearly associated with the prognosis. Many reports have stated that histological type and tumor grade are not correlated with the prognosis.[6-7,20]

Our study showed that patients with hematogenous metastasis to organs other than lung (bone, brain, liver) had a significantly poorer prognosis than those with metastasis only to lung. The median survival period of the patients with hematogenous metastasis to organs other than lung was 10.5 months and the longest survival was only 13 months. The direct cause of death was a new metastasis to other sites in bone, liver, or pericardium, suggesting the presence of extensive hematogenous metastasis. As for the favorable prognosis of the patients with lung metastasis, we speculate that the sensitivity to chemotherapy of distant metastases at different sites is different, and that lung metastasis may be most sensitive to chemotherapy; however, a greater number of patients is needed to prove this speculation statistically.

Paraaortic lymph node (PAN) metastasis is thought to be an important prognostic factor in endometrial cancer. In the present study, PAN metastasis was diagnosed in five patients. The distant PAN metastases were found in the supraclavicular lymph node in three patients, in the lung in two patients, and bone in one patient; and intraperitoneal dissemination was found in one patient). PAN metastasis had no impact on the prognosis, as determined by multivariate analyses ($P = 0.061$, data not shown).

The PS is likely related to the spread of tumor metastases. Bristow et al.[8] reported that the pretreatment PS was an important factor associated with the prognosis in advanced endometrial carcinoma. In patients with a good PS, extensive cytoreductive surgery is possible, any residual tumors can be reduced to optimal size, and postoperative adjuvant therapy can be performed aggressively. Therefore, even in patients with non-lung hematogenous metastasis, surgery should be selected if the PS is good and surgery is possible.

In conclusion, preoperative chemotherapy or radiotherapy in stage IVB endometrial carcinoma did not improve the prognosis, but a favorable prognosis was obtained in patients in whom surgery was possible as an initial treatment. In addition, reducing the residual tumor size to less than 2 cm by surgery appeared to contribute to a better prognosis. In a background evaluation of tumor spread, hematogenous metastasis to sites other than lung was a significant factor indicating poor prognosis, so effective multidisciplinary treatment methods need to be developed for such metastases.

Conflict of interest statement

No author has any conflict of interest.

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ORIGINAL ARTICLE

High serum alanine aminotransferase levels for the first three successive years can predict very high incidence of hepatocellular carcinoma in patients with Child Stage A HCV-associated liver cirrhosis

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Abstract

Objective. To assess retrospectively whether continuously high serum alanine aminotransferase (ALAT) levels (<80 IU) in the first three successive years after the diagnosis of liver cirrhosis (LC) are predictive of a subsequent high incidence of hepatocellular carcinoma (HCC) in patients with Child Stage A hepatitis C virus (HCV)-LC. ***Material and methods.*** The study comprised 132 HCV-LC (Child Stage A) patients who had not received interferon therapy but had been treated with anti-inflammatory agents. At the end of a 3-year follow-up after the diagnosis of LC, the patients were subdivided into three groups according to their serum ALAT levels and the subsequent incidence of HCC was assessed. ***Results.*** The cumulative incidence of HCC starting from 3 years after the diagnosis of LC in the continuously high ALAT group (annual average over 3 years always ≥80 IU; n=41; Group A) was markedly higher than that in the continuously low ALAT group (always <80 IU; n=48; Group B) (p<0.005) during an observation period of 7.9±3.7 years. The incidence of HCC in Group A was 11.8%/year. The odds ratios of developing HCC in Group A and Group C (mixed high and low ALAT levels; n=43) were 5.1-fold and 1.5-fold that of Group B, respectively. A multivariate analysis revealed that the ALAT group was independently associated with HCC development. ***Conclusions.*** Continuously high ALAT levels for three successive years following the diagnosis of LC can be predictive of a very high incidence of HCC in Child A HCV-LC patients. Prospective trials using therapeutic approaches aimed at decreasing ALAT levels are necessary in order to confirm a positive impact of ALAT reduction on the incidence of HCC in patients with HCV-LC.

Key Words: *Hepatitis C virus-associated liver cirrhosis, hepatocellular carcinoma, incidence of hepatocellular carcinoma, risk of hepatocellular carcinoma, serum alanine aminotransferase*

Introduction

Among the many hypotheses proposed to explain the pathogenesis of carcinoma, one is that repeated inflammation and the resulting increased proliferation (mitotic activity) of tissue cells are correlated with the development of carcinoma, presumably by chromosomal instability, an increased rate of random mutations [1,2], and promotion of tumor growth [3,4]. Moreover, with regard to the relationship between

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continuous inflammation and tumor promotion, Vasiliev & Moizhess [5] reported that the growth of a small number of tumor cells was stimulated when they were inoculated on or close to the surface of a polymer film. They suggested that host reactions such as inflammation may cause or promote tumorigenesis or tumor growth. Subsequently, Hamada et al. [6] succeeded in converting ER-1, a weakly tumorigenic cloned cell line of a rat mammary carcinoma, into a highly tumorigenic and metastatic cell line by interaction with host cells reactive to a foreign body (plastic plates). There are many reported clinical instances that demonstrate the relationship between continuous inflammation and carcinogenesis: *Helicobacter pylori* infection and gastric cancer [7,8], ulcerative colitis and colorectal cancer [9], *Clonorchis sinensis* infection and cholangiocellular carcinoma [10,11], and so on.

Considering the above findings, it is possible that the same mechanism is involved in the development of human hepatocellular carcinoma (HCC) and that the development of HCC is accelerated by continuous inflammation in the liver of patients with hepatitis C virus (HCV)-associated liver cirrhosis (LC). However, it is widely accepted that fibrosis may accelerate the development of HCC in HCV-associated liver diseases [12,13].

We previously demonstrated [14] the strong association between sustained high serum alanine aminotransferase (ALAT) levels (≥80 international units (INU) annual average) and the development of HCC in patients with HCV-LC (Child Stage A [15]) by long-term observation lasting about 7 years. However, the stage of LC at which inflammation strongly affects the development of HCC remained unclear. In this retrospective study, we focused on the first 3 years after the diagnosis of Child Stage A LC. That is, the effects of continuously high ALAT levels (≥80 IU) for 3 successive years following the diagnosis of LC on the subsequent development of HCC were observed in this study.

Material and methods

Study population

At the start of the study, patients who had previously been exposed to the hepatitis B virus, and patients who were positive for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody were excluded from the study. Patients who had previously undergone hepatic resection for HCC were also excluded. Patients who had previously been treated with interferon (INF) were also excluded. Of the 179 HCV-LC patients who were either anti-HCV positive (as confirmed by C-100 antibody or second-generation antibody) or HCV-RNA positive (as confirmed by polymerase chain reaction), 25 habitual alcohol drinkers were excluded. This group included patients who consumed >40 g of ethanol daily and those who drank alcohol >3 days per week. Of the remaining 154 patients with pure HCV-associated LC, 3 patients who died within 3 years of the study, and 19 patients who developed HCC within 3 years of the diagnosis of LC (Child Stage A) were also excluded, as it was speculated that HCC cells had already developed in the liver at the time of diagnosis of LC in these patients.

The study was confined to patients with Child Stage A [15] HCV-LC, because long-term follow-up is required to observe the occurrence of HCC. Most of the patients were hospitalized for liver biopsy diagnosis at Kanagawa Cancer Center Hospital, Kumamoto University Hospital, or Kitasato University Hospital between 1 April 1990 (when the estimation of HCV antibody became possible in our hospitals) and 31 January 1995.

The diagnosis of cirrhosis was made by liver biopsy for most of the patients (87 out of 132, 65.9%), but in some cases it was made on a clinical basis using ultrasound (US, 21, 15.9%), computed tomography scans (CT), biochemical tests (serum albumin level, zinc turbidity test, ASAT/ALAT ratio), and platelet counts. This study was carried out according to the Declaration of Helsinki; all patients provided written informed consent, and the study protocol was approved by the Human Research Review Committee of each hospital. The enrollment date for each patient was the date of diagnosis of LC in all cases.

The annual average of serum ALAT levels, starting from the date of diagnosis of LC, was calculated for all patients. For this calculation, 12 measurements were usually included, because the patients generally received a consultation once a month at our hospitals. Patients whose estimation of serum ALAT levels was incomplete for any year were omitted.

At the end of the 3-year follow-up, we divided the patients into three groups, and the subsequent incidence of HCC was observed: continuously high ALAT group (annual average over 3 years always ≥80 IU), continuously low ALAT group (annual average over 3 years always <80 IU), and intermittently high ALAT group (mixed high and low average ALAT levels, unclassified group). The reason 80 IU was adopted as a cut-off level was because the annual average ALAT level of patients with HCV-associated cirrhosis with high DNA synthesis activity of hepatocytes estimated by BrdU uptake [16] *in vitro* (BrdU labeling index (LI) ≥1.5%) that was shown in our

previous study [17] to have a high risk of developing HCC was found to be >80 IU in all patients [18]. The incidence of HCC starting 3 years after the diagnosis of LC was compared retrospectively among the groups. This comparison was made to examine the precise effect of inflammation in the first three years after diagnosis on the subsequent development of HCC in HCV-LC patients.

Follow-up study

Upon admission, most patients underwent a liver biopsy, and US and either magnetic resonance imaging (MRI) or computed tomography CT scans were carried out in all cases to exclude patients who already had HCC. After the patients were discharged, they were examined by US every 3 months and MRI or CT scans every 6 months to detect the presence of small HCC nodules. Serum α-fetoprotein (AFP) levels (radioimmunoassay <15.0 ng/ml) were measured, and biochemical tests, including serum albumin, serum ALAT, serum aspartate aminotransferase (ASAT), the thymol turbidity test, the zinc turbidity test, and peripheral blood counts were assessed every month. The patients were followed carefully during the long-term observation period, and endoscopic examination of esophageal varices was performed every 6–12 months in all patients. If esophageal varices with signs of redness were found, then either sclerotherapy or ligation therapy was carried out to prevent esophageal bleeding. If the US, CT, MRI, or AFP studies suggested the development of HCC, then further imaging examinations, including helical dynamic CT scans, lipiodol-CT [19], and angiography, were carried out to confirm the diagnosis of HCC. In particular, all patients with suspected development of HCC underwent angiography and Lipiodol infusion into the hepatic artery.

Out of the 80 cases that developed HCC in this study, HCC was confirmed histologically in 49 (61.3%) (hepatectomy in 40, biopsy in 9).

Therapeutic procedures

Stronger-neo-minophagen C (SNMC) [20] and Shosaiko-to [21] are herbal medicines used throughout Japan to treat chronic viral liver diseases. They act by reducing inflammatory processes [22] and controlling ALAT levels. Ursodeoxycholic acid (UDCA) [20] is also known to suppress elevated ALAT levels in some cases. Suzuki et al. [20] observed a significant decrease in serum ALAT levels by i.v. injection of SNMC in patients with chronic hepatitis, and Hirayama et al. [21] observed a significant decrease in serum ALAT levels by p.o. administration of Shosaiko-to to patients with chronic active hepatitis. Moreover, Bellentani et al. [23] observed a significant decrease in serum ALAT levels by long-term p.o. administration of UDCA to patients with chronic hepatitis. Furthermore, we recently showed a significant decrease in serum ALAT levels by combination therapy with these drugs in patients with HCV-associated cirrhosis [24].

For all patients in this study, we made an intensive effort to maintain average serum ALAT levels below 80 IU using one of the above-mentioned anti-inflammatory agents or a combination of these agents. The choice of agent was determined according to which was most effective for suppressing serum ALAT levels in each patient.

Statistical analysis

A total of 132 cases were followed up for >5 years, and were subdivided into three groups: the continuously high ALAT group, the continuously low ALAT group, and an unclassified (intermittently high) ALAT group. Demographic comparison of the three groups was done by one-way ANOVA or the Mann-Whitney test, according to data distribution.

Results

The results are presented as mean values (SD) or frequency (%) of descriptive statistics. The contingency table was analyzed with the χ^2 test. The differences in the risk of HCC incidence among the continuously high ALAT group (n=41) and the intermittently high ALAT group (n=43) as the reference of the continuously low ALAT group (n=48) were calculated by logistic regression [25].

The cumulative incidences of HCC in the three groups were analyzed taking into consideration the competing risks [26] using the Kaplan-Meier method [27] and the log-rank test. All analyses were two-tailed, and p-values of less than 0.05 were considered statistically significant. The statistical analyses were done on a personal computer using the statistical package SPSS for Windows (version 13.0; SPSS, Chicago, Ill. USA).

Finally, 132 patients with post-hepatic cirrhosis at Child Stage A [15] who had not received INF therapy were enrolled in this retrospective study. The characteristics of the 132 patients included in the study and the 49 excluded subjects at the beginning of the study are summarized in Table I. The reason for the