なかった’としている.

　一方, がん臨床医に対する調査でも, 経済的負担についての説明を, ‘必ずする’または‘たいていする’との回答は1/4であり, 過半数は‘説明をあまりしない’としている.

　このように, 経済面の説明は極めて不十分な状況にあることから, 費用に関するデータベースの整備や, 患者説明を支援するツールの開発は喫緊の課題と考えられる. そこで, 患者説明を支援するツールとして, 医師向けの費用ナビゲーション・システムの開発を進めており, 最近, その試作品が完成した.

　これは, 診療支援のパソコン画面に, 患者の性・年齢, 保険の種類, がんの部位, ステージ, 転移の有無, 治療法などを入力(選択)することで, 標準的な治療における平均的な医療費(自己負担額)が表示されるものである. この画面を参考にすれば, 多忙な臨床現場においても, 患者に経済面の必要な説明を行うことが可能になると考えられる.

2. がんの医療費

a. 国民医療費に占めるがん医療費

　平成17年度のがんの医療費は, 2兆5,748億円で, 一般診療医療費の10.3%を占める.

　部位別の医療費は, 厚生労働省の‘国民医療費’には公表されていないので, 患者調査, 社会医療診察行為別調査により推計した. 総数では, がん医療費に占める割合が高いのは, 肺癌(12.0%), 胃癌(11.1%), 結腸癌(9.8%), 乳癌(8.8%), 肝癌(7.2%), 直腸癌(5.6%)などの順である.

　男女別にみると, 男性では, 肺癌(14.8%), 胃癌(13.1%), 結腸癌(9.1%), 肝癌(9.0%), 前立腺癌(8.2%)などの順, 女性では, 乳癌(19.3%), 結腸癌(10.6%), 肺癌(8.6%), 胃癌(8.6%), 子宮癌(5.8%)などの順である.

b. 我が国の cost of cancer

　がん医療の経済的な意味は, cost of cancer でみることができる. cost of cancer は, がんの医療費(直接費用)と, がんの罹患や死亡による逸失利益(間接費用)の合計である[5]. これは, が

ん対策の投資効果と, がん医療の進捗状況を経済面から評価する指標であり, 効果的ながん医療の推進と, これに必要な財源を確保するための基礎資料といえる.

　逸失利益は, がんの罹患(morbidity cost), 死亡(mortality cost)で生じる, 本来得られるはずの生産性(賃金嫁得額)の経済的損失として算定する. がんで生じる痛みや苦悩の代価としての精神的・社会的費用は推計が容易でないため, 間接費用には含めないことが多い. がんの医療費(直接費用)は, 抑制すべき(財政当局)と, 増やすべき(医療提供側)との相反する立場があるが, がんによる逸失利益の削減については異論はないと考えられる.

　我が国の cost of cancer を, 人口動態調査, 国民医療費, 患者調査, 国勢調査, 労働力調査を用いて算定すると, 平成17年の場合, 9兆9,179億円と推計される. 内訳は, 医療費が2兆5,748億円, 入院および外来受診による逸失利益が5,563億円, 早期死亡による逸失利益が6兆7,868億円である.

　部位別にみると, 肺癌は, 医療費が3,101億円, 療養による逸失利益が735億円, 死亡による逸失利益が1兆2,238億円で, 合計1兆6,074億円となり, 最も高額である. 胃癌は, 各2,856億円, 735億円, 1兆300億円で, 合計1兆3,891億円であり, 肺癌に次いで高額である. その他主要な部位の cost of cancer をみると, 肝癌が9,912億円, 結腸癌が7,970億円, 直腸癌が4,984億円, 乳癌が5,597億円, 前立腺癌が2,709億円, 子宮癌が2,108億円などである.

　がんとともに, 我が国の三大死因である心疾患, 脳血管疾患について同様に試算を行うと, 各3兆4,423億円, 4兆1,028億円となる. 心疾患, 脳血管疾患と比較してみても, がんの逸失利益, とりわけ, 早期死亡による逸失利益は群を抜いて多いことがわかる. 第3次対がん総合戦略で示された, 死亡率の2割削減という目標の達成は, 必要性も緊急性も極めて高いといえる.

　がんの逸失利益を最少化するには, がんの予防, 早期発見と早期治療, 有効な治療法の開発

とともに，良質で効率的ながん治療の推進が欠かせない．がんによる社会的損失を減少させるためには，有効ながん対策であれば，10兆円からの巨額の資源投入を行うことも社会経済的に許容されうることが示唆される．

---

3. がん医療の経済分析

---

a. 経済分析の手法

がんの臨床医を対象に，がん医療の経済分析に関する意識調査(n=1,703，回答率24.3％)を実施したところ，がん医療を評価する場合，臨床面，QOL面，経済面の重要度は，全体を100％として，各59.0％，26.5％，14.5％(平均値)という結果であった．そして，将来は，これらは44.6％，35.5％，19.9％になることが望ましいと回答していた[6]．臨床面と，QOLプラス経済面とが，半々の重要度をもつことになる．

医療の経済評価は，医療に投じられた資源，すなわち，人，物，サービスまたはそれらが換算された費用と結果とのバランスを評価するものであり，代表的な分析法として，費用便益分析(cost-benefit analysis: CBA)，費用効果分析(cost-effectiveness analysis: CEA)，費用効用分析(cost-utility analysis: CUA)の3つがある．医療の経済分析は，医療費の抑制を目的にしたものではなく，医療の無駄や判断ミスを防ぎ，より質の高い医療を実現するための意志決定の補助手段である．

b. 費用便益分析

がん治療への資源投入量と得られる成果とのバランスシートを明らかにするには，入口と出口をともに貨幣で比較する，費用便益分析が有用である．そこで，主要な7種のがんについて，がん検診から確定診断，各種の治療を経て，回復または死亡に至る複雑な臨床経過を類型化し，Markovモデルに準じたシステムモデルを開発した[6]．

モデルのパラメータには，罹患数，死亡数，がん発見時のstage分布，stage別の治療法の選択，5年生存率，進行の確率など，渉猟しうる各種のデータを用いた．そして，がん診療に係る生涯医療費を費用，生存期間における労働生産性(賃金稼得額)を便益として，費用便益分析を行った．一部のデータはばらつきが大きかったが，有理Bezier曲線による補正を行うことで，より現実的なモデルの構築が可能となった．

モデルからは，がん治療のstage別，治療法別，転帰別に，我が国の患者数，期待生存年，QALYs(quality-adjusted life years)当たり医療費の増分，費用便益比などが算出される．また，近い将来にがんの罹患率や死亡率(5年生存率)が変化(改善)した場合の，費用便益比の変化，PYLL(potential years of life lost)の変化などのシミュレーションが可能となる．

その結果，例えば5年生存率が1％改善すると，男性の胃，肺，大腸，前立腺癌の費用便益比は各1％，2.5％，1.6％，−0.6％増加する．生存率の改善による費用便益比の増加幅は胃，乳房，子宮癌よりも肺，大腸癌で大きくなる．また，罹患率の変化による費用便益費の将来推計を行うと，大腸でその減少幅が大きいことがわかる．

おわりに

がん対策基本法には，患者に等しく適切ながん医療を提供することが謳われており，患者の身体的，精神的な悩みに加え，経済的な悩みにも十分な対応をしなくてはならない．技術進歩などに伴う高額な薬剤・機器の導入によって，患者の経済的な負担は更に大きなものになる恐れがある．がん医療の経済分析は，患者の経済的負担を最少化しつつ，優れたがん医療を実践するための意志決定の補助手段としてその重要性が増している．

また，患者数増加や技術革新などによって，がん医療には今後も多くの医療資源が消費されることが予想される．社会からは，莫大な資源投入が正当化されるための根拠(evidence)とそれに相応しい結果(outcome)が求められている．がん医療の長足の進歩に見合う医療資源を引き続き確保するには，がん医療の経済貢献を明らかにするなど，国民的合意を促すためのわかりやすい説明を丁寧に行っていく必要があると思われる．

■文　　献

1) 濃沼信夫：厚生労働科学研究費補助金　第3次対がん総合戦略研究事業「がんの医療経済的な解析を踏まえた患者負担最小化に関する研究」平成19年度総括・分担研究報告書, 2008.

2) 濃沼信夫：厚生労働科学研究費補助金　第3次対がん総合戦略研究事業「がん医療経済と患者負担最小化に関する研究」平成18年度総括・分担研究報告書, 2007.

3) 濃沼信夫：厚生労働科学研究費補助金　第3次対がん総合戦略研究事業「がん医療経済と患者負担最小化に関する研究」平成17年度総括・分担研究報告書, 2006.

4) 濃沼信夫：がん患者の経済的負担について. 血液・腫瘍科　53(4): 427-435, 2006.

5) Brown ML, Yabroff KR: Economic impact of cancer in the United States. In: Cancer Epidemiology and Prevention, 3rd ed(ed by Schottenfeld D, Fraumeni JF), p202-214, Oxford University Press, New York, 2006.

6) 濃沼信夫：がん対策の費用対効果. Geriatric Medicine　42(5): 579-586, 2004.

がんの医療経済

要旨

　患者中心医療の要請、技術革新の進展、医療資源の制約などから、臨床的根拠とともに経済的根拠に基づくがん医療を実践することがますます重要となっている。経済的理由で治療の中止や変更を余儀なくされる患者（1% 以下）が生じてきており、質の高いがん医療をあまねく提供するには、臨床現場での配慮、現行制度の弾力的運用、がんにかかる医療制度の抜本改革が強く求められる。がんによる経済的な損失は約 10 兆円と疾病の中で群を抜いて多く、がん対策に優先的に多くの資源配分を行うことは合理性がある。

はじめに

　2009 年 8 月，米国臨床腫瘍学会（ASCO）は，2007 年に設置した特別委員会（Cost of Cancer Care Task Force）の検討を踏まえ，がんの費用に関する指針を発表した[1]．この背景には，分子標的治療，粒子線治療など，日進月歩の技術進歩で次々に登場する高額ながん医療が，時に患者に重い経済的負担となり，治療成績に影響を与えかねないという危機感がある．

　この指針は，費用を検討することは質の高いがん医療の重要な要素であるとし，① 高騰するがん医療費の影響について，がん臨床医の認識を高める，② 適切な臨床判断が行えるよう，がんの費用に関する患者・家族との対話を促す，③ がん医療の経済面に関し，ASCO が主導的に提言しうる政策を明確化することを目指したものである．

　米国は，国民医療費が国内総生産（GDP）の 16% を占め，2017 年には 20% に達すると見込まれること[1]，人口の 6 分の 1 にあたる 4,700 万人もの無保険者の存在が深刻な健康格差をもたらし，オバマ政権はこの解消を狙う抜本的な医療保険改革を最優先で進めていることなど，我が国とは医療を巡る状況が大きく異なる．しかし，我が国

● キーワード

がん医療費
cost of cancer
費用効果分析
QALY
患者自己負担

においても，患者と国家の経済的な問題は，がん対策基本法に謳うが
ん医療の進歩を患者にあまねく届けるうえで大きな障害となりつつあ
る．

　本稿では，胃がんに焦点を当てつつ，がんの医療経済について最近
の知見を踏まえながら概説する．

10兆円の経済損失

　我が国のがん医療費は2兆6,958億円（2007年度，一般診療医療
費）で，国民医療費34兆1,360億円に占める割合は7.9％，一般診
療医療費25兆6,418億円に占める割合は10.5％である．国民医療費
の対前年度比が3.0％増加であるのに対し，がん医療費の伸びは
7.9％である．

　がんによる経済的な損失は，個人と社会にとっても大きなものであ
り，がん医療費（直接費用）として計上される金額にとどまらないは
ずである．すなわち，がんに罹患することで失われる生産性（mor-
bidity cost），がんで平均余命よりも早死にすることによる逸失利益
（mortality cost）などの間接費用は相当な金額に違いない．死の恐怖
や家族や友人を失う精神的な苦痛など，がん罹患に伴う非金銭的な損
失も少なくないと思われる．

　これら直接費用と間接費用（非金銭的な損失は含めず）を合計した，
がんの経済的損失（cost of cancer）を，人口動態統計，国勢調査，
総務省日本統計年鑑などを用いて試算すると，年間9兆6,822億円と
なる[2]．これは直接医療費2兆5,748億円（2005年度）に，入院の
morbidity cost 4,182億円，通院の morbidity cost 1,275億円，早期
死亡の mortality cost 6兆5,617億円を加えたもので，GDPの2％
に匹敵する金額である．

　米国の cost of cancer は，2008年は2,281億ドル（約21兆円，医
療費932億ドル，morbidity cost 188億ドル，mortality cost 1,161億
ドル）と推計されている[3]．最近の円高・ドル安傾向による為替の変
化などで単純な比較はできないが，米国の cost of cancer は我が国の
ほぼ2倍の水準にある．

　胃がんの cost of cancer は，医療費3,191億円（2005年度），入院
の morbidity cost 548億円，通院の morbidity cost 174億円，mor-

tality cost 9,909 億円を合わせた，1 兆 3,822 億円と推計される．がんの部位別医療費は公表されていないので，胃がんの医療費は，人口動態調査，患者調査，社会医療診療行為別調査を用いて推計したものである．

Cost of cancer は，国民に対して，がんの予防と診療の意義について理解と認識を高めるのに有用であるともに，がん医療の経済評価にも用いられる．例えば，cost of cancer に占める mortality cost の割合は，全部位で 68％ であり，部位別では，肺 76％，胃 72％，乳房 56％ などである．胃がんの mortality cost の割合はやや大きく，生存率のさらなる向上，特に 59 歳以下の患者の救命が課題であることが医療経済の観点からもうかがえる．

米国におけるがんの mortality cost は，2020 年に 1,476 億ドルに達すると予測され，肺，大腸，乳房，膵臓，脳の各がん，および白血病の死亡率を年間 1％ 減少させることができれば，経済損失を年間 8 億 1,400 万ドル削減できるとの推計がある[4]．

また，cost of cancer は，政策決定において，がん対策に優先的に多くの資源配分行うことの合理的な根拠ともなる．すなわち，同様の方法で，ほかの疾病について経済的損失を試算すると，心疾患は 3 兆 5,797 億円，脳血管疾患は 1 兆 7,954 億円，糖尿病は 1 兆 1,166 億円などとなり，がんの経済的損失が最も多いことが分かる．

40万円の自己負担

がん患者は身体的，精神的な負担と共に経済的な負担を強いられる．高額療養費制度などで，患者負担が過大とならないための制度はあるが，ほかの疾病と同じく，かかった費用の一定割合が自己負担となるので，病状が重いほど経済的負担も重くなる．がん患者の経済的負担については，断片的な情報にとどまるので，患者自身に領収書や家計簿を見ながら実際の支出額を記入してもらう方式で実態を把握した[5]．

結果をみると，がん患者の平均自己負担額は，年間 100.7 万円にのぼっている（n＝6,604，粒子線治療の患者を除く）．内訳は，直接費用として，入院 51.9 万円（該当割合 74.4％），外来 18.1 万円（100％），交通費 4.5 万円（93.7％）である．また，間接費用として，健康食品・民間療法 21.7 万円（56.8％），民間保険料 25.3 万円（85.1％），

その他 13.8 万円（42.5％）である．平均自己負担額は，各項目を平均額に該当割合を乗じて加算したものである．

　一方，償還・給付される金額は，平均 62.5 万円であり，内訳は，高額療養費 28.3 万円（該当割合 52.6％），税の医療費還付 8.6 万円（23.2％），民間保険給付 101.8 万円（44.8％）である．これらから，実質の平均的な負担額は，自己負担額から償還・給付額を差し引いた，38.2 万円と想定される．退職年齢を過ぎ（回答者の平均年齢 63.3 歳），長期間の療養が必要となることが多いことから，この負担額は重く感じられる．

　胃がん患者（n＝706）では，平均の自己負担額は 76.6 万円，償還・給付額は 50.1 万円で，実質の年間負担額は 26.5 万円である．

　治療法別にみると，化学療法における実質の平均負担額は 57.9 万円（n＝1,150，自己負担 133.1 万円，償還・給付 75.2 万円），放射線治療は 51.9 万円（粒子線治療を除く，n＝1,419，各 129.8 万円，77.9 万円），粒子線治療は 304.5 万円（n＝388，各 420.4 万円，115.9 万円）である．化学療法，放射線治療，粒子線治療でより重い自己負担となっている．

　また，がん経験者（cancer survivor，n＝1,153，平均年齢）の年間の自己負担額は，平均 23.3 万円で，内訳は，入院 26.1 万円（該当割合 39.8％），外来 3.8 万円（97.5％），民間保険料 16.3 万円（51.9％），民間療法 12.4 万円（5.7％）である．民間療法で支出が多いのは，ワクチン，キトサン，フコイダン，AHCC（各 1 ～ 3％）などである．償還・給付の平均額は 10.8 万円で，民間保険給付金（11.9％）が最も多い．がん経験者の実質の負担額は，年間 12.5 万円と算出される．

　がん臨床医（n＝691）を対象にした調査[6]から，経済的理由で治療の中止や変更を余儀なくされる患者は，がん患者全体の 1％以下（入院 0.83％，外来 0.05％）と推計される．新しい治療技術の導入に伴うがん医療の高額化により，今後，こうした経済問題が顕在化する恐れがある．調査では，治療の中止・変更は，比較的高額な抗がん剤で多い．

経済的根拠の要請

　患者中心医療の要請，技術革新の進展，医療資源の制約などから，臨床的根拠（clinical evidence）と共に経済的根拠（economic evidence）に基づく医療を実践することの重要性は，世界的に認識されつつある．英国の NICE（National Institute for Clinical Excellence）を始め，欧米の関係機関で，医療経済的な評価を含む技術評価のガイダンスが進められている．

　がん医療の経済評価は，一般の医療の経済評価と同じく，投じられた資源，すなわち人，物，サービスまたはそれらが換算された費用と結果とのバランスを評価するものである．代表的な分析法として，費用効果分析（cost-effectiveness analysis），費用効用分析（cost-utility analysis），費用便益分析（cost-benefit analysis），費用最小化分析（cost-minimization analysis）がある．医療の経済分析は，医療費の抑制を目的にしたものではなく，医療の無駄や判断ミスを防ぎ，より質の高い医療を実現するための意志決定の補助手段である．

　最近，がんの臨床現場には有効であると同時に高額な治療法が多く登場するようになって，従来の枠組みを越えた経済評価が必要となっている．世界の抗がん剤の使用量は，2005 年は 250 億ドル（うち米国が 160 億ドル，次いで多いのが日本と EU 諸国）であるが，2025 年までに市場規模が 3,000 億ドル（約 27 兆円）に膨張するとの予測[7]もある．

　費用効果分析の結果で，社会が容認しうる閾値は，米国では 1 QALY（質を調整した生存年）あたり 5 万ドル（約 450 万円）程度と考えられてきた[8]が，最近は，これを上回る薬剤が登場するようになり，使用を推奨するかどうかの評価が容易でなくなってきている．経済分析のデータはそれを実施した条件が異なるので，単純な比較はできないが，例えば乳がんに対する分子標的薬トラスツズマブに関する経済評価の文献を分析すると，該当する 16 件のうち半数は 1 QALY あたり費用が 5 万ドルを超えている．

　経済的根拠が強く求められるがん分子標的薬に関し，臨床現場での経済評価を行った文献数は，最近 10 年間で 332 件を数えるが，費用効果分析などを用いて検討がされたものはいまだ限られている．我が

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

文献

1) Meropol N J, et al: American Society of Clinical Oncology Guidance Statement: The cost of cancer care. J Clin Oncology 27: 3868-3874, 2009.
2) 濃沼信夫, 他: わが国の cost of cancer. 日本医療・病院管理学会誌 45 Suppl: 68, 2008.
3) American Cancer Society: Cancer Facts & Figures 2009. Atlanta, 2009.
4) Bradley C J, et al: Productivity costs of cancer mortality in the United States: 2000-2020. JNCI 100: 1763-1770, 2008.
5) 濃沼信夫: 厚生労働科学研究費補助金 第 3 次対がん総合戦略研究事業「がんの医療経済的な解析を踏まえた患者負担最小化に関する研究」平成 20 年度総括・分担研究報告書. 2009.
6) 濃沼信夫: 厚生労働科学研究費補助金 第 3 次対がん総合戦略研究事業「がん医療経済

と患者負担最小化に関する研究」平成 17 年度総括・分担研究報告書. 2006.

7) Bosanquet N, et al: The economics of cancer care. p91-111. Cambridge Univ Press, New York, 2006.

8) Neumann PJ: Using cost-effectiveness analysis to improve health care. p116-137.

Oxford Univ Press, New York, 2005.

9) Koinuma N, et al: Economic motivation for behavior modification to undergo the cancer screening. 68th Annual Meeting of JCA Proceedings 507-508, 2009.

10) 濃沼信夫: がん検診推進に税控除を. 日医新報 4412: 1, 2008.

ORIGINAL ARTICLE

Reiko Numazaki · Etsuko Miyagi · Katsuyuki Konnai
Masae Ikeda · Akihito Yamamoto · Ryo Onose
Hisamori Kato · Naoyuki Okamoto · Fumiki Hirahara
Hiroki Nakayama

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

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

R. Numazaki · K. Konnai · M. Ikeda · A. Yamamoto · R. Onose · H. Kato · H. Nakayama
Department of Gynecology, Kanagawa Cancer Center Hospital, Yokohama, Japan

E. Miyagi (✉) · F. Hirahara
Department of Obstetrics and Gynecology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
Tel. +81-45-787-2691; Fax +81-45-701-3536
e-mail: emiyagi@med.yokohama-cu.ac.jp

N. Okamoto
Department of Epidemiology, Kanagawa Cancer Center Research Institute, Yokohama, Japan

* R. Numazaki and E. Miyagi contributed equally to this study.

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/m²; cyclophosphamide 500 mg/m²; pirarubicin 30 mg/m²) was administered to patients from 1985 to 1998, and the TC regimen (paclitaxel 175 mg/m²; 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
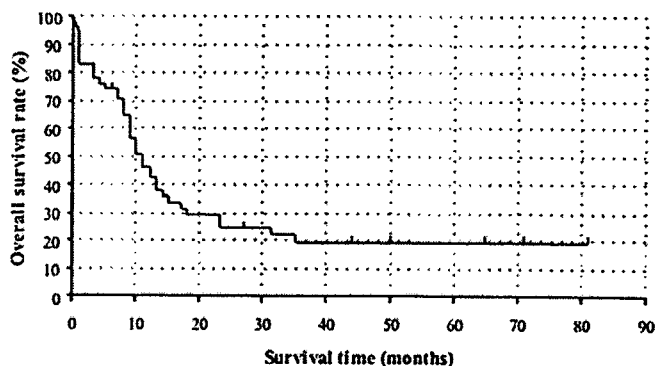

Fig. 1. Overall survival rate of all 55 patients with stage IVB endometrial carcinoma

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.

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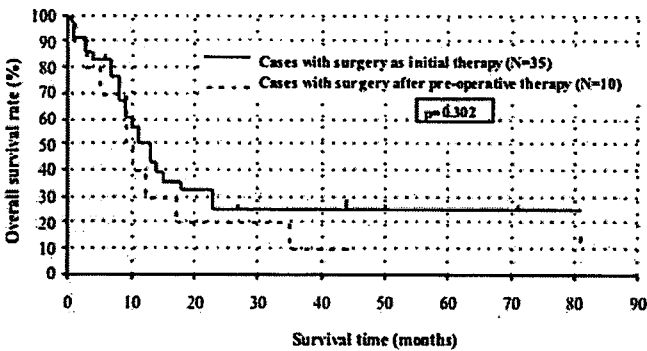
Fig. 2. Overall survival rates of the 35 patients who underwent surgery as the initial treatment and the 10 patients who underwent surgery after radiotherapy or chemotherapy as the initial treatment
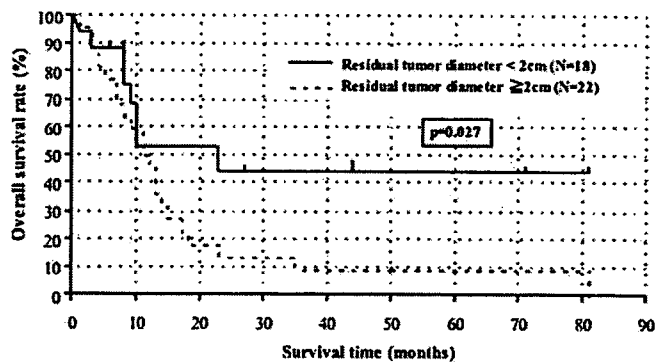

Fig. 3. Overall survival rates of the 22 patients with a residual tumor diameter of 2 cm or more and the 18 patients with a residual tumor diameter less than 2 cm

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),
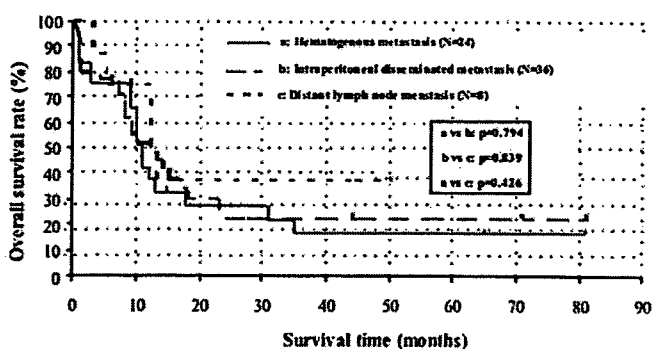

Fig. 4. Overall survival rates of the 24 patients with hematogenous distant metastasis, the 36 patients with intraperitoneal disseminated metastasis, and the 8 patients with distant lymph node metastasis

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
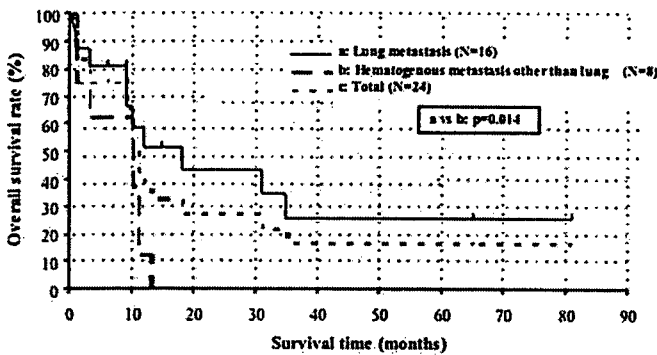CI, confidence interval; NS, not significant

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.

References

1. Landis SH, Murray T, Bolden S, et al. (1999) Cancer statistics 1999. CA Cancer J Clin 49:8-31
2. Pecorrelli S, Creasman WT, Pettersson F, et al. (1998) FIGO annual report on the results of treatment in gynecologic cancer. J Epidemiol Biostat 3:35-62
3. Wolfson AH, Sightler SE, Markoe AM, et al. (1992) The prognostic significance of surgical staging for carcinoma of the endometrium. Gynecol Oncol 45:142-146
4. Marino BD, Burke TW, Tornos C, et al. (1995) Staging laparotomy for endometrial carcinoma. Assessment of peritoneal spread. Gynecol Oncol 56:34-38
5. Vardi JR, Tadros GH, Anselmo MT, et al. (1992) The value of exploratory laparotomy in patients with endometrial carcinoma according to the new International Federation of Gynecology and Obstetrics staging. Obstet Gynecol 80:204-208
6. Goff BA, Goodman A, Muntz HG, et al. (1994) Surgical IV endometrial carcinoma: a study of 47 patients. Gynecol Oncol 52: 237-240
7. Chi DS, Welshinger M, Verkatraman RR (1997) The role of surgical cytoreduction in stage IV endometrial carcinoma. Gynecol Oncol 67:56-60
8. Bristow RE, Zerbe MJ, Rosenshein NB, et al. (2000) Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 78:85-91
9. Kaplan EL, Meier P (1958) Non-parametric estimation for incomplete observations. J Am Stat Assoc 53:457-481

10. Mantel N (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163–170

11. Snedecor GW, Cochran WG (1980) Statistical methods, 6th edn. Iowa State University Press, Ames, IA

12. Le TD, Yamada SD, Rutgers JL, et al. (1999) Complete response of a stage IV uterine papillary serous carcinoma to neoadjuvant chemotherapy with taxol and carboplatin. Gynecol Oncol 73: 461–463

13. Compagnutta E, Giorda G, De Piero G, et al. (2004) Surgical treatment of recurrent endometrial carcinoma. Cancer 100:89–96

14. Greven K, Olds W (1987) Radiotherapy in the management of endometrial carcinoma with cervical involvement. Cancer 60: 1737–1740

15. Grigsby PW, Pertz CA, Camel HM, et al. (1985) Stage II carcinoma of the endometrium: results of therapy and prognostic factors. Int J Radiat Oncol Biol Phys 11:1915–1923

16. NCCN practice guidelines in oncology v.1.2005. Uterine cancers. http://www.nccn.org/professionals/physician

17. Landgren RC, Fletcher GH, Delclos L, et al. (1976) Irradiation of endometrial cancer in patients with medical contraindication to surgery or with unresectable lesions. AJR Am J Roentgenol 126: 148–154

18. Pliskow S, Penalver M, Averette HE (1990) Stage III and IV endometrial carcinoma: a review of 41 cases. Gynecol Oncol 38:210–215

19. Aalders JG, Aberler V, Kolstad P (1984) Stage IV endometrial carcinoma: a clinical and histological study of 83 patients. Gynecol Oncol 17:75–84

20. Behbakht K, Yorden EL, Casey C, et al. (1994) Prognosis indicators of survival in advanced endometrial cancer. Gynecol Oncol 55:363–367

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

KAORU MIYAKAWA[1,2], KAZUO TARAO[2], KENJI OHSHIGE[3], SOICHIRO MORINAGA[1], SHINICHI OHKAWA[1], NAOYUKI OKAMOTO[4], AKITAKA SHIBUYA[5], SHIGERU ADACHI[5], YUKIKO MIURA[5], SHIGETOSHI FUJIYAMA[6], SHIHO MIYASE[6] & KIMIO TOMITA[7]

[1]Department of Gastroenterology, Kanagawa Cancer Center Hospital, Yokohama, Japan, [2]Tarao's Gastroenterological Clinic, Yokohama, Japan, [3]Department of Public Health, Yokohama City University, Yokohama, Japan, [4]Research Institute, Kanagawa Cancer Center, Yokohama, Japan, [5]Department of Gastroenterology, Kitasato University, Sagamihara, Japan, [6]Department of Gastroenterology, NTT West Kyushu Hospital, Kumamoto, Japan, and [7]Department of Nephrology, Kumamoto University, Kumamoto, Japan

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