におけるtaxane系薬剤とplatinum系薬剤の位置付けを確立する必要があり，本邦においてもAP療法を標準治療としてTC療法またはDP療法（DOC＋CDDP）の優位性を検証するランダム化第Ⅲ相試験（JGOG2043）が，GOGにおいてはTAP療法v.s. TC療法のランダム化第Ⅲ相試験（GOG209試験）が進行中であり，その結果が待たれる．また，内分泌療法については，現時点でのエビデンスは乏しいものの，今後多くの臨床試験で検討されるべき治療法である．われわれは常に臨床試験の動向を注視し，また，積極的に参加する姿勢が求められている．

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Osteoporosis Japan

子宮体がん術後患者における骨密度の特徴に関する検討

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はじめに

子宮体がんは近年増加の一途をたどっている。近年，40歳未満の若年発生例の増加が指摘されているが[1]，厚生労働省がん研究助成金「地域がん登録」研究班の報告によると，子宮体がんの総罹患率が著しく上昇しているとともに，罹患率の構成が変化し生殖年齢層でも多くの発生がみられ，以前から提唱されている閉経前後にピークを認めるという概念が変化してきている(**図1**)。

子宮体がんの標準的治療は手術療法であり，ほぼ全症例で両側卵巣摘出術が行われる(**表1**)。卵巣由来の女性ホルモンは骨粗鬆症や脂質代謝異常症の主因としてきわめて重要な意義があるが，近年の子宮体がん罹患の低年齢化や罹患率の急速な増加，さらには術後補助療法の改良が奏効の改善をもたらしたことにより，今後非担がんで卵巣摘出された患者の増加が考えられ，大きな問題となることが容易に想像される。

そこでわれわれは，子宮体がん術後患者にお

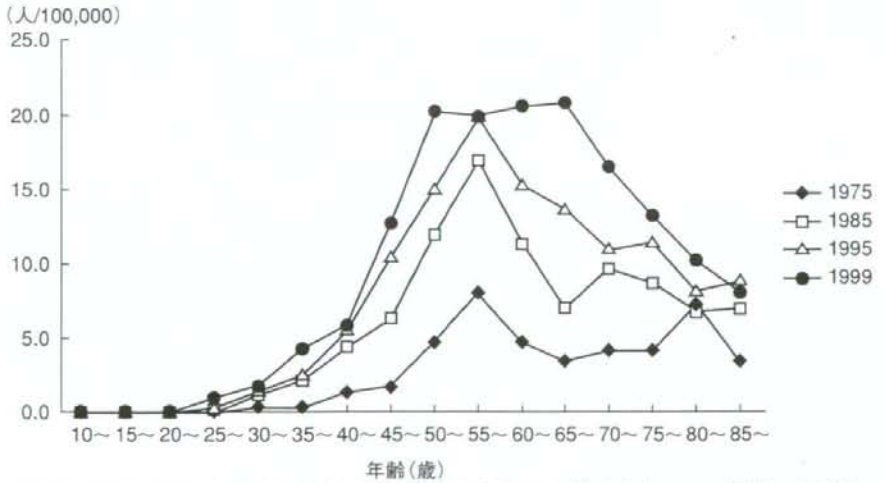

図1　子宮体がんの年齢別罹患率の推移（厚生労働省がん研究助成金による「地域がん登録」研究班より）
総罹患率が著しく上昇しているとともに，罹患率の構成が変化している(1975～1999年)。

慶應義塾大学医学部 産婦人科

表1　慶應義塾大学病院産婦人科における子宮体がんの手術療法
手術施行ほぼ全例で両側卵巣摘出を行う。

子宮摘出術式	
Ⅰ期が推定される場合	単純子宮全摘出術または準広汎子宮全摘出術
Ⅱ期が推定される場合	広汎子宮全摘出術
Ⅲ期が推定される場合	準広汎子宮全摘出術 (がんが頸部に及んでいる可能性がある場合は広汎子宮全摘出術)
リンパ節郭清範囲	
骨盤内リンパ節	原則として郭清
傍大動脈リンパ節	手術時所見(肉眼±迅速病理)にて下記のいずれかが確認されれば郭清筋層浸潤が1/2以上, G3類内膜癌, 漿液性腺癌, 明細胞腺癌付属器転移陽性, 骨盤リンパ節転移陽性

表2　体がん群と対照群の例数, 平均年齢および範囲

	例数	平均年齢(歳)(範囲)
体がん群	132	60(30～85)
対照群	224	56(41～82)
計	356	

ける骨粗鬆症の至適管理法を確立することを究極目的として, まず子宮体がん術後患者における骨代謝の特徴について自然閉経例との比較検討を行った。

1　対象と方法

対象は当院産婦人科にて初回治療として両側卵巣摘出術を伴う手術療法を施行した子宮体がん症例132例(体がん群)と当科健康維持外来に受診した非担がん自然閉経症例224例(対照群)の計356例で, 各群の平均年齢と範囲を**表2**に示した。

これらの症例に対して, 日本骨代謝学会の診断基準に準じて第2～第4腰椎の平均骨密度値(L_{2-4}BMD)より骨粗鬆症および骨量減少を診断した。そのうえで, それらの結果を体がん群および対照群の2群間で比較検討することで子宮体がん症例における骨密度の特徴を検討した。さらに子宮体がん症例において卵巣摘出時における閉経の有無と骨粗鬆症/骨量減少の発症頻度についても比較を行った。

2　結　　果

体がん群において, 骨粗鬆症/骨量減少と診断できた症例は132例中35例(27%), 対照群では224例中90例(40%)であり, 体がん群では骨量正常例が有意に多い($p < 0.05$)ことが判明した(**図2**)。また, 卵巣摘出時の閉経の有無により, 骨粗鬆症/骨量減少の発生頻度に有意差を認めなかった(**表3**)。

3　考　　察

骨粗鬆症治療のエンドポイントは, 老齢者の骨折予防にあり, 当然のことながら子宮体がん術後患者においてもあてはまる。

子宮体がん患者と骨折の関係については, 以前より相反する関係が指摘されている。1992年にPerssonらは子宮体がん例では, 大腿骨頸部骨折のリスクが低いことを報告している[2]。一方, 子宮体がん患者と骨密度との関係についても, 1999年にDouchiらは, 子宮体がん例のBMD値は非担がん対照群と比較し有意に高値であることを指摘している[3]。また最近でもデンマークにおいて, 23,935例の各種がん罹患者

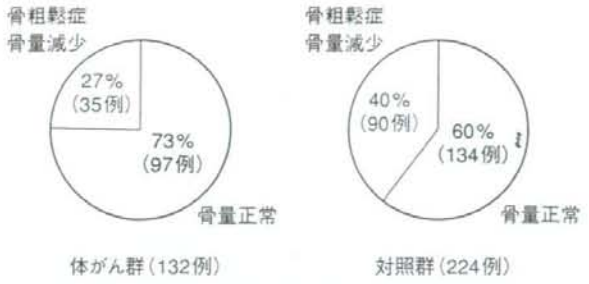

図2　体がん群と対照群における骨密度測定結果
体がん群では骨密度正常例が有意に多いことが判明した
($p < 0.05$)。

を対象として骨密度測定を施行した報告によると，子宮体がん罹患者は70歳未満例，および70歳以上例の両者においても骨粗鬆症と診断される割合が，非担がん対照群と比較してそれぞれ約6割と低率であったとしている[4]。今回のわれわれの結果も，これらの報告と同じ傾向が示された。

元来，子宮体がんの発生に対しては，エストロゲンの関与が指摘されており，これらの報告を総合すれば，持続的な高エストロゲン状態が卵巣摘出後の骨密度の低下を抑制している可能性が示唆される。

しかしながら，発症頻度は低くても，骨粗鬆症に罹患する患者は少なからず存在するため，術後早期からの介入が必要ないわけでは決してなく，長期的なフォローアップを行うことがこれらの患者のquality of life(QOL)の向上に役立つことはいうまでもない。

おわりに

今回の検討からは，子宮体がん例は卵巣摘出を施行しているにもかかわらず，骨粗鬆症/骨量減少の高危険群とはいいがたいことが判明した。しかしながら近年，若年発症例が増加していることからも，長期にわたる慎重なフォローアップが必要であると考えられた。また近年，乳がんで使用されているアロマターゼ阻害薬投与により，骨塩量が低下することが問題になりつつあるが，わが国でも子宮体がん治療においてアロマターゼ阻害薬を使用する臨床試験が行われており(適応外)，当該症例については乳がん患者同様に骨密度測定による慎重な管理が必要であると考えられる。

表3　子宮体がん症例における卵巣摘出時の月経の有無と，骨粗鬆症/骨量減少の発症頻度

	骨粗鬆症/骨量減少	骨密度正常
閉経前	15	42
閉経後	20	39

$p = 0.374$
卵巣摘出時の閉経の有無により，骨粗鬆症/骨量減少の発生頻度に有意差を認めなかった。

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特集 子宮がんの治療指針

4．子宮がん患者へのインフォームドコンセント(IC)

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View Points !

▶がん告知は十分な組織学的根拠が得られてから慎重に行う。

▶がん告知は患者と家族が同席する場で行い，診療録にその説明内容を記載する。特に妊孕性温存の可否，妊娠中の子宮頸がん発症時の妊娠継続の可否，卵巣機能温存の可否などの説明には，詳細な evidence の説明，選択決定のための反復説明も必要となる場合がある。

▶病態説明や治療法選択に関しては，口頭だけでなく書面でも情報提供を行い informed consent を得ることが望ましい。

- 子宮がんは子宮頸がんと子宮体がんに大別される。本稿では，早期の子宮頸がんまたは子宮体がんと診断された患者に対してインフォームドコンセント（IC）を行う際における重要点ならびに注意すべき点についてその要点を述べる。

がん告知について

- がん告知については様々な論議はあるものの，現在は原則患者本人にありのままの検査結果と病態を説明した上で，治療の選択肢について詳細に説明を行い，患者に治療法を選択してもらうという流れが広く受け入れられている。しかしながら，患者本人のみへの説明では，精神的動揺により説明内容が十分には理解・記憶されず，誤解を生じて逆に治療の妨げになることもあり得る。
- 特に，近年は子宮頸がん発症年齢の若年化が進み，10～20歳代の浸潤癌例にも遭遇する。
- 子宮体がんは罹患総数が増加しているため，20～30歳代の異型内膜増殖症や Ia 期推定の類内膜癌症例も増加傾向にある。
- 未婚の若年患者に対するがん告知は，妊孕性の問題や患者本人の学業・結婚・就職という問題も加わるため，慎重に行う必要がある。
- 患者がひとりで外来に来院されている場合は，がんの可能性が高いので詳しい検査が必要で次回外来に家族と共に来院するように，と勧め，後日の機会で詳しく説明するという段取りを踏むことも場合によって必要であろう。
- また，告知とそれに続く病態や治療の説明内容は，その場で診療録に可及的に詳細に記載し，後日に説明内容について医師・患者間で齟齬をきたさぬように十分留意する必要がある。
- 確実な組織診上のがん診断が得られておら

ず，細胞診や画像診断で疑いがあるという段階ではあくまでがんの可能性がある（否定できない）という説明にとどめる慎重さが必要である。

- 女性にとって重要な妊孕性温存に関わる卵巣や子宮温存の可能性について，または妊娠中にがんが発見された場合の妊娠継続の可否についての説明に際しては，十分な検査結果に基づき，最新の evidence を集めた上で，患者本人と配偶者・家族とともに妊孕性温存や妊娠継続の可否や危険性について説明を行うことが重要である。
- 患者本人のみに説明を行った場合には，妊孕性温存・妊娠継続を強く希望する患者が説明内容を家族に伝える際に，妊孕性温存・妊娠継続の demerit に関する情報提供が十分に行われず，バイアスがかかった家族間協議に陥ってしまう可能性があるからである。一度の説明では患者側の疑問点が整理されず納得されないまま判断を下さざるを得ないことにもなりかねないので，書面での説明を加えたり，必要に応じて，反復説明および疑問点への回答を行ったりすることも患者からの信頼を得るために重要であろう。
- 閉経前の患者に対して，標準治療として医師側からは当然と判断される両側付属器切除術や骨盤照射が必要な場合でも，術後または照射後に生じ得る女性ホルモン欠落症状（更年期障害），骨粗鬆症などについて確実に説明しておくことが求められる。何故なら，治療前の患者側の意識は生命の危険について集中されるため，更年期障害について意識が回らず，重度の症状が生じた場合は QOL が損なわれ，患者側には治療に対する不満が残り，その後の補助療法や follow up が的確に行われづらくなることもあるからである。

Evidence について

- 基本的には，各病態に対して，日本婦人科腫瘍学会編の子宮頸癌治療ガイドライン2007年版[1]または子宮体癌治療ガイドライン2006年版[2]，NCCN の子宮頸癌ガイドライン[3]，子宮体癌ガイドライン[4]などに記載されている標準治療について説明をまず行う。
- まず，標準治療を行った場合の治療効果と合併症について説明し，次に，何も治療を行わなかった場合の経過予測を，さらに標準治療以外の治療を行った場合の治療効果と合併症にも言及した上で，患者および家族に治療法を選択してもらうことになる。
- 合併症については，その重症度と頻度に関する情報はできるだけ具体的に客観的説明を行うことが，患者が不必要な不安を感じず，より的確な治療法選択を行う手助けとなる。
- 標準治療がまだ定まっていない病態に対しては，複数の治療法をまず同列に客観的に説明し，その上で主治医としてどの治療を勧めるのか，その理由を説明すべきであり，またこのような場合は標準治療を定めるべく prospective な無作為比較試験が多施設で行われていることが多いので，その臨床試験に参加することの意義，メリットとデメリットを説明する。また自施設で提供できない治療法についても情報提供を行う必要がある。
- 近年は，患者は internet 上で様々な専門的情報にアクセスすることも可能になっている一方で，多分にバイアスの入った他の患者からの情報に戸惑って来院されることもしばしば経験される。様々な evidence を誤りなく的確に患者に提供する姿勢がより強く求められる時代になっていると言えよ

う。

- 当教室では，基本的な病態や治療手技に対して，院内の安全対策室を通してリーガルアドバイザーの助言を得た上で，病態の説明と治療に関する説明文書と同意書を作成しており，可能な限り口頭と文書にて患者に説明を行い，質問とそれに対する回答は診療録に記載を行っている。
- 以下に早期の子宮頸がんと子宮体がんの主な病態におけるICの要点をのべる。詳細は他稿を参照されたい。

子宮頸がん

1．上皮内癌

- 組織診にて上皮内癌と診断された場合，妊孕性温存希望がなければ単純子宮全摘出または円錐切除術を行い，妊孕性温存希望がある場合は子宮頸部円錐切除術を標準治療として説明する。
- 日本産科婦人科学会婦人科腫瘍委員会報告[5]によると，2006年では79%の症例に対して円錐切除術が選択されている。説明すべき要点を列挙する。
- 最終病理診断では少なからず微小浸潤癌が確認される場合や，高齢者の場合は頸管内の高い位置に病変が存在することがあり，円錐切除術で病変が切除しきれず子宮全摘出が必要となる場合もある。
- まれにskip lesionが残存する可能性があること，完全摘出例でも再発の可能性がある。
- 当科治療成績では，まれに（約2%）子宮口閉鎖または狭窄により子宮口開口手術や開大処置が必要となる場合や，手術中または直後に出血多量となり輸血または子宮摘出を余儀なくされた例が0.2%に認められている。
- 術後1～2週間後に月経量以上の再出血が生じることもあり，緊急受診の必要性については夜間祝日は当直医と電話で相談していただく必要がある。
- 妊娠に至った場合は早産になり得る可能性が約20%の症例に生じ，円錐切除を受けていない場合の9%よりかなり高い頻度となっている。
- 妊娠中に細胞診，コルポスコピー診，組織診にて総合的に上皮内癌までと診断された場合は，妊娠中は円錐切除術を施行せず分娩後まで待機することも可能である。
- 光線力学療法（PDT療法）はまだ広く普及しているとは言い難い状況である（当科では施行していない）が，切除を行わない点で出血がきわめて少なく早産の危険性がないことではメリットがある一方，最終病理診断が得られないことや光過敏症が生じるため日常生活に支障をきたすデメリットも有する。光感受性物質の改良により過敏症の軽減が図られているが，まだ標準療法には至っていない。PDT療法を希望する患者に対しては治療を実施している他施設にsecond opinionとして紹介している。

2．微小浸潤癌

- コルポスコピー下狙い組織診にて術前に微小浸潤癌と判定された場合，Ia1期が推定される場合は，妊孕性温存希望症例では子宮頸部円錐切除を，温存希望がない場合は拡大子宮全摘出術を勧めている。しかしながら円錐切除術でIa2以上の病変が確認されたり，Ia1の範囲内であっても癒合浸潤や脈管侵襲が認められたり断端陽性である場合は子宮全摘出術が必要になることも説明している。
- Ia1期でも0～1%にリンパ節転移が認められることも事前に説明しておく。
- Ia2期が円錐切除標本で推定される場合

は，リンパ節転移頻度が0～10%と報告されていることから，骨盤リンパ節郭清が必要となる。当科では原則として広汎子宮全摘出（または準広汎子宮全摘出），両側付属器切除，骨盤リンパ節郭清を行っているが，妊孕性温存希望例では骨盤リンパ節郭清も併せ行う広汎性子宮頸部摘出術（Radical trachelectomy）を施行している。

- 当教室での適応基準は，①妊孕性温存希望がある，②不妊症でない，③Ia 2期からIb 1期までである，④腫瘍径が2 cm以下である（外向発育型で浸潤が浅い場合は2 cm以上でも適応とすることもある），⑤コルポスコピー・MRI検査にて内頸部浸潤は限局している，⑥転移を疑う所見を認めない，などである[6]。なお，子宮全摘出に伴う合併症の説明内容については次項の広汎子宮全摘出術の項で述べる。
- 妊娠中にIa期が疑われる場合には，診断確定のために円錐切除術が必要であり，妊娠継続希望があり，Ia 1期で脈管侵襲，癒合浸潤，がん遺残がなければ，円錐切除術で治療終了としてもよい。
- 上記以外のIa 1期であったり，Ia 2期であれば，胎児が体外生活が可能な時期であれば帝王切開で胎児を娩出し，同時に子宮頸がん根治術を行う場合が多い。体外生活が不可能な時期であれば，子宮頸がん手術の施行時期を延期する可能性を含めて，個々のケースに応じた慎重な検討が必要である。

3．浸潤癌Ib 1期

- Ib 1期が推定される場合は，標準治療である広汎子宮全摘出術（骨盤リンパ節郭清と両側付属器切除を含む）を勧めるが，放射線療法，同時化学放射線療法の選択肢もあり得ることを説明する必要がある。広汎子宮全摘出術施行の合併症については以下の点に留意し十分説明を行う必要がある。

①出血多量に対する輸血の可能性と輸血の合併症について

②尿管・膀胱・直腸など他臓器の術中損傷の可能性（1～2%）と，術後の尿管瘻・膀胱瘻発生の可能性（1～2%），水腎症の可能性（1%以下）とそれに対する治療について

③腹腔内または皮下の再出血の可能性（1%以下）と再開腹止血術の可能性について

④排尿障害については，子宮，膀胱，尿管，膀胱機能に関与する神経（下腹神経・骨盤内臓神経）について解剖学的に説明した上で，手術操作に伴う神経切断の可能性を説明する。術後しばらく尿意を感じない，尿が出ないまたは出にくい，などの症状が出ること，また症状改善には個人差があること，数年経過しても尿意を感じにくく（30%），軽症を含めると尿漏れが約50%あり得るという報告があること，自己導尿の必要性があり得ること，などである。また神経温存術式を施行してもこれらの合併症の可能性が0%になるわけではないことも言及しておく。

⑤軽度な排便障害が起こりうるものの下剤服用で改善されることがほとんどであること。

⑥リンパ浮腫（10～20%）に対してリンパマッサージや弾性包帯や弾性ストッキングによる予防が重要であること，下肢の傷や炎症に注意すること，リンパ嚢胞に対しては大きなものや炎症を併発したものにはドレナージ排液などの外科的処置が必要になり得ること，蜂窩織炎では入院して抗生剤投与を受ける必要があり得ること，などを説明しておく。

⑦下肢静脈血栓と肺塞栓の可能性が0.5～1％程度に認められ，それらに対する予防策として術中から下肢の血流を補助するエアマッサージャーを使用し，早期離床に心がける。

⑧腸閉塞は2～4％に認められ，術後放射線療法が加わるとこの頻度はさらに上昇する。術後早期離床が重要であり，発症した場合はチューブ留置による保存的治療をまず行うが，軽快が見られない，または反復する場合は腸閉塞解除術が必要になることもあり得る。

⑨予防的な抗生剤投与にもかかわらず，術後感染症が約10％に起こり得る。膿瘍が形成され抗生剤投与が奏効しない場合はドレナージ手術が必要なこともある。

- 準広汎子宮全摘出術では上記の排尿障害や排便障害の頻度が低くなり，広汎性子宮頸部摘出術後には，上記以外に，子宮頸管狭窄または閉鎖，子宮内感染，早産などのリスクが加わる。
- 妊孕性温存を希望される患者の場合は，前項微小浸潤癌で述べた広汎子宮頸部切除術の適応基準を満たすかどうかを具体的に検討し患者に判りやすく説明を行う。適応を満たす場合でも，腺癌では扁平上皮癌よりskip lesionが認められる頻度が高く，より慎重な適応検討が求められる。さらに，術中に腫大リンパ節が迅速病理検査にて転移陽性と判断され広汎子宮全摘出術へ変更される可能性があること，また術後にリンパ節転移が判明する場合は後療法を追加することも事前に十分に説明しておくことが必要である。
- 放射線療法，CCRTについても，合併症について婦人科側から，または放射線科医からも事前に説明を行うことが求められる。
- 卵巣機能温存希望の患者に対しては，扁平上皮癌での卵巣転移率は1％未満であるとする報告が多く卵巣温存は可能であるが，腺癌での卵巣転移率は数％とする報告があり，卵巣温存には慎重であるべきで，多数の症例を基にしたデータでの説明が望ましいと考えられる。

子宮体がん

1．子宮内膜異型増殖症

- 本邦では子宮体がん0期として分類されている複雑型子宮内膜異型増殖症に対しては，標準的治療として子宮全摘出が勧められる。これは，異型内膜増殖症が，前癌病変の性格を有すること，しばしば子宮体がんに伴うものであり，内膜組織診で子宮内膜異型増殖症と診断された症例の子宮全摘出術後の最終診断におけるがんの併存率は17～50％とされているからである。
- したがって，内膜組織診で子宮内膜異型増殖症と診断された場合は，上記を患者によく説明した上で静脈麻酔下で内膜全面掻爬を行いがんの共存の可能性を確認する必要がある。全面掻爬にて異型内膜増殖症までと診断されればリンパ節郭清の必要はないとしてよい。
- 妊孕性温存希望の症例に対しては，高用量黄体ホルモン投与と反復内膜全面掻爬により81～94％の奏効率が報告されている[8～10]。本邦では酢酸メドロキシプロゲステロン（MPA）のみが使用可能であるが，血栓症（約1％），肝機能障害（約1％），体重増加などの合併症にも言及しておく必要がある。治療に不応性で腺癌へ進行する場合もあり，その場合は子宮全摘出と両側付属器切除術が必要となることは十分説明しておく必要がある。

2．Ia 期推定

- 子宮内膜全面掻爬標本にてがん（腺癌，腺扁平上皮癌，癌肉腫，肉腫など）と診断された場合は，基本的に子宮全摘出術，両側付属器切除術，骨盤リンパ節郭清術が標準治療とされている。合併症で手術が施行できない場合以外は，手術に代わって放射線療法や化学療法を第一選択とするevidenceはない。
- 画像診断（MRI，CT）や子宮鏡検査にて子宮外進展や頸部進展が否定的である場合の子宮全摘出の術式としては，単純腹式子宮全摘出が選択されることが多く，筋層浸潤を伴う場合は準広汎子宮全摘出術が選択される施設もある。
- 摘出卵巣への転移率は，術前にⅠ期推定の場合は約5％，Ⅱ期推定の場合は約10％と比較的高く，また若年子宮体がんの場合は卵巣がん合併率は45歳未満で約29％と，45歳以上の約5倍高率であるという報告[11]もあり，Ⅰ期といえども安易に付属器を温存することは望ましくなく，慎重な情報提供と検討が必要と言えよう。
- 当科ではIa期推定の場合でも卵巣温存の危険性を十分説明し，原則として両側付属器切除を施行している。卵巣温存希望の患者にはsecond opinionを聞いた上で判断してもらうこともある。
- リンパ節郭清は，Ia期が推定される類内膜癌G1の場合のみに省略可能とされている[2]。当科のデータでは筋層浸潤が1/3未満のG1例での骨盤リンパ節転移頻度は約2％であり，術後初めて筋層浸潤が病理学的に確認された場合に，改めてリンパ節郭清を追加するかどうかの検討のためのデータとして情報提供している。なお，術後病理診断にて類内膜癌G2で筋層浸潤1/3未満例では約4％に，類内膜癌G1で筋層浸潤1/3から1/2の症例では約7％に，類内膜癌G2で筋層浸潤1/3から1/2の症例では約15％に転移を認めている。
- 画像診断（MRI，CT）にて筋層浸潤や子宮外進展が否定的である場合で，強い妊孕性温存希望がある場合は，高用量黄体ホルモン（MPA600mg/d）投与と反復内膜全面掻爬による保存的治療の適応となり得，53～100％の奏効率が報告されている[2,8,9]。しかしながら，子宮腔内に再発する可能性が高い（約50％程度）こと，重複がんとしての卵巣がんや腹膜がん症例があり得ること，病変消失後の排卵誘発の安全性にまだevidenceがないこと，など，まだ検討すべき余地が多い段階であることに留意して，十分な情報提供を行うべきである。
- また，病変消失後の定期的follow upが大切であることをよく説明しておかないと，未通院後の久しぶりの来院時に再発，子宮外転移を認める危険性もある。
- 妊孕性温存療法は，的確な病理診断，画像診断に基づいて行われる必要性があり，病理診断やMRI上筋層浸潤判定に悩む場合は積極的にsecond opinionを依頼して検討することが望ましい。
- MRIで筋層浸潤が疑われる病変が確認されない場合は，単純子宮全摘出と両側付属器切除が，Ia期が推定されても上記のように類内膜癌G1以外の組織型・分化度である場合は，子宮全摘出術，両側付属器切除術，骨盤リンパ節郭清が勧められる。

3．Ib 期以上

- 画像診断上，Ib期，Ic期，Ⅱa期，Ⅱb期が推定される症例に対しては，子宮全摘出，両側付属器切除，骨盤リンパ節郭清が標準治療である。子宮摘出方法としては，一般

的に単純子宮全摘出術が行われることが多いが，筋層浸潤を伴う症例には準広汎子宮全摘出術が選択される施設も多く，明らかに頸部間質浸潤を示す症例には広汎子宮全摘出術が望ましい。しかし，この準広汎，広汎子宮全摘出には術後排尿障害などの合併症(子宮頸がんの項で既述)を伴うため，拡大手術の必要性と demerit については術前に十分説明を行っておく必要がある。

- また，NCCN Clinical Practice Guideline では筋層浸潤の有無にかかわらず骨盤および傍大動脈リンパ節郭清を行うことを推奨している。一方，一定の条件の下で骨盤および傍大動脈リンパ節の生検を推奨している海外のガイドラインも存在する。
- 現時点では，傍大動脈リンパ節郭清を省略できるのは，類内膜腺癌 G1 または G2 相当で，筋層浸潤 1/2 以下，術中の観察で子宮外病変のみられない場合である[2]。

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Treatment of cervical cancer with adjuvant chemotherapy versus adjuvant radiotherapy after radical hysterectomy and systematic lymphadenectomy

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Abstract

Aim: To compare the clinical efficacy focused on post-treatment morbidity between adjuvant chemotherapy (CT) and pelvic radiotherapy (RT) after radical hysterectomy for patients with cervical cancer.

Methods: A total of 125 patients with cervical squamous cell carcinoma who underwent radical hysterectomy and pelvic lymphadenectomy at Hokkaido University Hospital between 1991 and 2002 were enrolled in the study for retrospective analysis. Seventy patients with recurrent risk factors, including deep stromal invasion, lymph vascular space invasion, parametrial invasion, lymph node metastasis (LNM), and bulky tumor (≥4 cm), received adjuvant therapy; 42 were treated with RT, and 28 were treated with CT. Almost all patients with multiple LNM received RT. Analyses were also performed on a subgroup of 50 patients without multiple LNM (23 RT, 27 CT). Clinical efficacy of post-treatment morbidity and survival was evaluated.

Results: Because there were more patients with multiple LNM in the RT group, we analyzed disease-free survival in 50 patients without multiple LNM. The 3-year disease-free survival rate was 82.6% with RT and 96.3% with CT ($P = 0.16$). Postoperative bowel obstruction was significantly more frequent in the RT group versus the CT ($P = 0.007$) and no-therapy ($P = 0.0026$) groups. Urinary disturbance was also more frequent in the RT group than in the CT ($P = 0.0016$) and no-therapy ($P = 0.089$) groups.

Conclusion: CT has the equivalent therapeutic effect as RT with fewer postoperative complications for patients with intermediate risks. A prospective randomized trial is needed to compare CT combined with radical hysterectomy and pelvic lymphadenectomy to RT or chemoradiotherapy.

Key words: adjuvant chemotherapy and radiotherapy, cervical cancer.

Introduction

Cervical cancer is generally treated by surgery, radiotherapy (RT), or a combination of the two. At many institutions in Japan, cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage Ib1-IIb) is treated with radical surgery and adjuvant RT when postoperative pathological examinations reveal risk factors for recurrence, including deep stromal invasion (DSI), lymph vascular space involvement (LVSI), parametrial invasion (PI), lymph node metastasis (LNM), and bulky tumor (tumor diameter >4 cm [BT]). We traditionally treated radical surgery first, and used RT as an adjuvant therapy for patients with stage Ib1-IIb disease. However, there is no definitive evidence that RT is beneficial after radical surgery for cervical cancer.[1,2] Adjuvant chemotherapy (CT) combined with radical hysterectomy and systematic lymphadenectomy may also provide a survival benefit. However, there are no randomized

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controlled studies comparing the clinical efficacy of CT and RT.

In our institution, adjuvant RT was used after radical hysterectomy. However, we observed severe postoperative complications (lymphedema, bowel obstruction and urinary disturbance) among patients receiving adjuvant RT that significantly reduced quality of life. Based on these observations and some data suggesting that the therapeutic effects of adjuvant CT and adjuvant RT were similar,[3] we began to use more frequent adjuvant CT after surgery after the year 2000. In the present retrospective study, we investigated the clinical efficacy of adjuvant RT and CT after radical and systematic lymphadenectomy in women with cervical cancer by comparing patient survival and postoperative complications.

Methods

One hundred twenty-five patients with FIGO stage Ib1-IIb cervical squamous cell carcinoma were treated at Hokkaido University Hospital between 1991 and 2002. All patients underwent radical hysterectomy with removal of a vaginal cuff of at least 2 cm, total resection of parametrial tissue and systematic retroperitoneal lymphadenectomy. This operation is a nerve-sparing modification of the Okabayashi operation.[4,5] The nerve-sparing procedure was further refined by introducing the preservation of vesical branches of pelvic plexus after 1997. Patients with risk factors for recurrence, including DSI (>2/3 thickness), LVSI, PI, LNM, and BT, received adjuvant RT or CT.

RT consisted of whole pelvic external irradiation by four-field technique with 50 Gy for 25 fractions beginning 4 weeks after surgery. Chemotherapy consisted of bleomycin (7 mg/body from days 1–5), vincristine (0.7 mg/m^2 on day 5), mitomycin C (7 mg/m^2 on day 5), and cisplatin (14 mg/m^2 from days 1–5). Patients received at least three courses at 4-week intervals beginning 2–3 weeks after surgery.

The patients' 3-year overall survival and disease-free survival were evaluated. We also assessed postoperative complications, including leg lymphedema, bowel obstruction and urinary disturbance. Patients with grade 1 leg edema were considered positive for lymphedema. Patients treated for bowel obstruction with intravenous infusion and/or surgery were considered positive for bowel obstruction. Patients with long-term self-catheterization or incontinence were considered positive for postoperative urinary disturbance.

Patient survival was calculated using the Kaplan–Meier method. The significance of the survival difference was evaluated using the log–rank test. The χ^2 test was used to analyze correlations between variables. Significance was set at $P < 0.05$. Statistical analyses were performed with the Statview software package (SAS Institute; Cary, NC, USA).

Results

Patient characteristics are listed in Table 1. Of the 125 patients who underwent radical hysterectomy, 83 patients had risk factors, 13 patients did not receive adjuvant therapy because four had post operative complications, and nine refused to receive adjuvant therapy. Forty-two of the patients with risk factors were treated with adjuvant RT between 1991 and 2000. In this group, the mean age was 50.3 years (range 28–74). Nine of the patients treated with adjuvant RT presented with clinical stage Ib1 cancer, 13 with stage Ib2 cancer, one with stage IIa cancer, and 19 with stage IIb cancer. Postoperative pathology examination confirmed that 24 patients had DSI, 35 had LVSI, 14 had PI, 16 had BT and 32 had LNM (19 cases had multiple LNM). Twenty-eight patients with risk factors for recurrence were treated with adjuvant CT between 2000 and 2002. Their mean age was 52.2 years (range 35–71). Eleven of these patients presented with clinical stage Ib1 cancer, nine with stage Ib2 cancer, two with stage IIa cancer, and six with stage IIb cancer. Postoperative pathology examination confirmed that 27 cases treated with adjuvant CT had some risk for recurrence; 11 had DSI, 27 had LVSI, five had PI, 10 had BT, and three had LNM. Only one case with multiple LNM received CT.

Treatment outcomes are shown in Table 2. In the RT group, 16 of 42 patients (38.1%) had recurrent disease and nine of 42 patients (21.4%) died due to disease of cancer. Seven patients had pelvic tumor recurrence affecting the vaginal stump, pelvic wall, or pelvic lymph node. Nine patients had extrapelvic recurrence affecting the lung, liver, brain, or supraclavicular lymph node. In the CT group, one of 28 patients (3.6%) experienced recurrence. The site of recurrence was the sacral surface, and the patient was alive with no evidence of disease after salvage radiation. The 3-year overall survival was 92.0% for the entire patient population, 98.2% for the patients not receiving adjuvant therapy, 100% for the CT group, and 78.5% for the RT group. The 3-year disease-free survival rate was 83.2% for the entire patient population, 92.7% for the patients

Table 1 Characteristics of 125 patients treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy

	No treatment	Adjuvant therapy		*P*-value
		Radiotherapy	Chemotherapy	
No. patients	55	42	28	
Age	49.0 (28–76)	50.3 (28–74)	52.2 (35–71)	NS
Stage				NS
Ib1	26	9	11	
Ib2	5	13	9	
IIa	1	1	2	
IIb	23	19	6	
LVSI	13	35	27	NS
Depth of stromal invasion				NS
<2/3	49	18	17	
≥2/3	6	24	11	
Parametrial invasion	2	14	5	NS
Bulky tumor	0	16	10	NS
Pelvic lymph node metastasis				0.0001
0	54	10	25	
1	1	13	2	
≥2	0	19	1	

LVSI, lymph-vascular space invasion; NS, not significant.

Table 2 Outcome of 125 patients at 3 years after surgery, according to type of adjuvant therapy

Adjuvant therapy	No. patients	NED	Recurrence site (pelvic, distant)	DOD
No treatment	55	52	3, 0	1
Radiotherapy	42	26	7, 9	9
Chemotherapy	28	27	1, 0	0
Total	126	105	11, 9	10

DOD, dead of disease; NED, no evidence of disease.

not receiving adjuvant therapy, 96.4% for the CT group, and 61.9% for the RT group.

Because multiple LNM was more frequent in the RT group than in the CT group, we repeated the above analyses on 50 patients without multiple LNM. There was no statistically significant difference between the RT and CT patients with regard to clinical stage, DSI, LVSI, BT or PI. Single-node metastasis was more frequent in the RT group. The 3-year disease-free survival rate was 82.6% in the RT group and 96.3% in the CT group (Fig. 1); the difference was not statistically significant ($P = 0.16$).

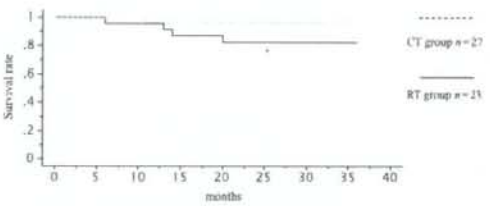

Figure 1 Three-year disease-free survival in 50 cases without multiple lymph node metastasis according to type of adjuvant therapy. CT, adjuvant chemotherapy; RT, pelvic radiotherapy.

The incidences of postoperative complications are shown in Table 3. Among the 55 patients who did not receive adjuvant treatment, eight (14.5%) had leg lymphedema, five (9.1%) had grade 1 bowel obstruction, and 12 (21.8%) had urinary disturbance. Among the 42 patients who received adjuvant RT, 12 (28.6%) had leg lymphedema, 16 (38.1%) had urinary disturbance, and 13 (31.0%) had bowel obstruction. Nine bowel obstructions were cured by conservative treatment, two required insertion of an ileus tube, and two necessitated intestinal surgery. Among the 28 patients in the CT group, four (14.3%) had leg lymphedema, one (3.6%) had grade 1 bowel obstruction, and two (7.1%)

Table 3 Rate of incidence of complications according to type of adjuvant therapy

Adjuvant therapy	No. patients	Data unavailable	Lymphedema	Bowel obstruction	Urinary disturbance
No treatment	55	7	8 (16.7%)[a]	5 (9.1%)[d]	12 (21.8%)[g]
Radiotherapy	42	4	12 (31.6%)[b]	13† (31.0%)[e]	16 (38.1%)[h]
Chemotherapy	28	0	3 (14.3%)[c]	1 (3.6%)[f]	2 (7.1%)[i]
Total	125	11	24 (19.2%)	19 (15.2%)	30 (24.0%)

Two cases required intestinal surgery. Lymphedema, a versus b: $P = 0.086$, b versus c: $P = 0.090$. Bowel obstruction, d versus e: $P = 0.007$, e versus f: $P = 0.0026$. Urinary disturbance, g versus h: $P = 0.089$, h versus i: $P = 0.0016$, g versus i: $P = 0.052$.

had urinary disturbance. The incidence of lymphedema tended to be higher in the RT group versus the other groups, but the difference was not statistically significant. Urinary disturbance was more frequent in the RT group versus the CT group ($P = 0.0016$) and no therapy group ($P = 0.089$). The incidence of bowel obstruction was significantly higher in the RT group than in the patients not receiving adjuvant treatment ($P = 0.007$) and in the CT group ($P = 0.0026$).

Discussion

A difference in the distribution of patients with lymph node metastasis across the treatment groups was found in this study, and we examined 50 patients without multiple LNM. We investigated the effect of adjuvant therapies after radical surgery in patients with intermediate risk factors for recurrence because it has been reported that multiple LNM has an effect on patient survival.[6–10]

Radical hysterectomy and radical RT for invasive cervical cancer are performed with the intent to cure the patient. However, these treatments can be associated with significant morbidity. Surgical complications are prevalent shortly after treatment, while complications of RT often occur years later. Combining these radical treatments increases the risk of complications compared to either treatment alone.[11–13] Regarding quality of life, radical hysterectomy has advantages over RT in terms of sexual function in young women with cervical cancer.[14] However, postoperative bladder dysfunction (neurogenic bladder) is a major disadvantage of radical hysterectomy. Recent attempts to avoid this complication with nerve-sparing surgical techniques have significantly decreased the risk of postoperative bladder dysfunction.[15–17] However, postoperative RT may extinguish the advantages of surgical therapy. As an alternative, some data support the clinical usefulness of CT as an adjuvant setting after radical hysterectomy.[18]

The most important prognostic factors of cervical cancer include parametrial extension of a cancer, positive surgical margins, and lymph node metastasis. Survival of node-positive patients is further affected by the site and number of positive nodes. An analysis in patients without multiple LNM revealed no significant difference in 3-year disease-free survival in CT versus RT. Although it has been suggested that adjuvant CT combined with radical hysterectomy and systematic lymphadenectomy has a survival benefit,[19] the role of adjuvant CT alone has not been extensively investigated.[18] In order to reduce the morbidity that may be caused by aggressive multimodality therapy, it seems important to conduct randomized trials to verify the effectiveness of this strategy.

The type of surgery is another important factor when considering adjuvant therapy. Japanese gynecologic oncologists use the Okabayashi operation and its modification, which correspond to type IV radical hysterectomy in the Piver-Rutledge classification. The extent of lymphadenectomy is also an important factor. Recent publications have shown that the number of lymph nodes removed is related to the survival of patients with various types of cancer, including breast, bladder, colon, and endometrial cancers, suggesting the therapeutic importance of systematic lymphadenectomy. Pieterse *et al.* found a significant relationship between the number of removed lymph nodes and the survival of cervical cancer patients with positive nodes.[20] Adjuvant RT is probably useful for eradicating tumor cells in unresected lymph nodes; we have evidence that postoperative pelvic radiation reduces the local recurrence of tumors at the cost of increased morbidity.

The failure pattern differs across adjuvant therapies. Adjuvant RT reduces local recurrence but not distant metastasis.[21] Adjuvant CT does not reduce local recurrence,[22] but reduces distant metastasis.[23] In the present study, there was a trend toward a difference between RT and CT in this regard, although not significant, because RT arm included more frequent cases with multiple LNM as a prognostic factor.

There was increased incidence of urinary disturbance and bowel obstruction in the RT group versus

the other groups. The incidence of postoperative interstitial complications with adjuvant RT was reported as 35.5% by Els *et al.*[24] and 48% by Bye *et al.*[25] Thus, radical hysterectomy followed by adjuvant RT results in a higher rate of bowel complications than CT.

Because of the non-randomized design of the study, we cannot draw any conclusion regarding the respective effects of the two adjuvant treatment modalities on overall survival. However, we can conclude that the effect of CT on disease-free survival was no worse than that of RT for patients without multiple LNM, and was associated with fewer bowel complications. Therefore, we believe that it is worth considering a prospective randomized trial of CT versus RT as an optional adjuvant therapy to patients with intermediate risk factors for recurrence.

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Midkine and its clinical significance in endometrial carcinoma

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Midkine (MK) is a secreted heparin-binding growth factor. Several types of human cancer have increased MK expression with elevated serum levels. The purpose of this study was to determine whether MK was expressed in endometrial carcinoma and to evaluate the clinicopathological significance of serum MK in patients with endometrial carcinoma. Immunohistochemical expression of MK was evaluated in 85 endometrial carcinoma samples and 33 controls. MK expression was significantly higher in the carcinomas than in normal endometrium ($P < 0.001$). Interestingly, MK expression was highest at the margins of invasion and low in the superficial areas of the tumor samples. Using ELISA, we compared serum MK concentration in 120 endometrial carcinoma patients with the concentration in 46 patients with benign gynecologic tumors. Serum MK value in patients with cancer was significantly higher than that in the patients with benign diseases ($P = 0.01$). Patients with positive lymph node metastasis or recurrence, or cancer death, had a higher serum MK level ($P = 0.008$, $P = 0.009$, respectively). In conclusion, MK immunoreactivity in endometrial carcinoma is significantly higher than in normal endometrium. Additionally, preoperative serum MK levels are significantly correlated with prognosis and the presence of lymph node metastasis. Thus, MK may be a useful serum biomarker for identifying high risk patients of endometrial carcinoma. (*Cancer Sci* 2008; 99: 1125–1130)

Endometrial carcinoma is one of the most common female pelvic malignancies worldwide, and its incidence has recently increased in Japan.[1,2] As approximately 80% of endometrial carcinomas are diagnosed at an early stage when surgery is curative, they carry a better prognosis than other cancers. However, advanced or recurrent cases tend to respond poorly to conventional treatments such as radiation, chemotherapy, or hormonal therapy, and as a result carry a poor prognosis. Identification of additional prognostic markers could help detect patients at a high risk of relapse or death from the disease.

Clinical, biological, and epidemiological findings all suggest that prolonged or unopposed estrogenic stimulation increases the risk of type I endometrial carcinoma. The initiation and progression of type I endometrial carcinoma, however, are poorly understood at a molecular level. We previously studied the gene expression profile of endometrioid adenocarcinoma, and identified 24 genes that had at least a 1.5-fold increased expression in both well (grade 1) and poorly (grade 3) differentiated endometrioid adenocarcinoma compared to normal endometrium (unpublished data). MK was identified as one of the up-regulated genes. Though MK expression has been reported in many human cancers, it has not been studied in endometrial carcinoma. Therefore, we focused our subsequent experiments on the actions of MK.

MK is a secreted, heparin-binding growth factor. It is a 13-kDa protein rich in basic amino acids and cysteine.[3,4] MK is highly expressed in the mid-gestational period during embryogenesis, and is involved in tooth, lung, kidney, and bone development. In the adult, MK has a very restricted pattern of expression. The highest transcript levels are in the intestine with low levels in the cerebellum, thyroid, kidney, bladder, lung alveoli, colon, stomach, and spleen.[5] The pathophysiological effects of MK include the oncogenic transformation of fibroblasts, antiapoptotic activity, and angiogenic activity.[6–8] MK mRNA levels and protein expression are frequently elevated in various human carcinomas of the breast, lung, esophagus, colon, ovary, urinary bladder, and prostate; and glioblastomas, neuroblastomas, and Wilms' tumor.[9–18] Furthermore, MK concentrations in serum are also elevated in various carcinomas.[19–22] To our knowledge, however, no study has focused on the clinicopathological significance of MK expression in human endometrial carcinoma. The purpose of this study was to determine whether MK was expressed in endometrial carcinoma, and whether differences existed between the expression level in cancer and levels in benign gynecologic conditions. We also explored whether correlations existed between MK expression and clinicopathological features.

Materials and Methods

Tissue and serum samples. Eighty-five endometrioid endometrial carcinomas (37 well differentiated, 25 moderately differentiated, 23 poorly differentiated; 55 stage I, 16 stage II, 11 stage III, three stage IV) were retrieved from the surgical pathology files of Tohoku University Hospital, Sendai, Japan for immunohistochemical analysis. The controls were selected from patients who underwent hysterectomy for benign gynecologic diseases without any personal cancer history from April 1996 to March 2004. The median follow-up time for patients whose samples were examined immunohistochemically was 60 months (range, 2–148 months). The disease-free and overall survival times of the patients were calculated from the time of initial surgery to recurrence or death, or the date of last contact. The survival times of patients still alive or lost to follow-up were censored in December 2004. Serum samples were obtained from 120 patients with endometrial carcinoma (66 well differentiated, 16 moderately differentiated, 12 poorly differentiated, 26 other histological type; 80 stage I, 11 stage II, 17 stage III, 12 stage IV) and from 45 patients with non-malignant gynecologic diseases at Tohoku University Hospital from April 2002 to January 2007. None of the patients examined had received radiation, hormonal therapy, or chemotherapy prior to surgery. The median follow-up time for the patients whose serum was tested for MK was 91 months (range, 1–166 months). The

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survival times of patients still alive or lost to follow-up were censored in August 2007. The protocol for this study was approved by the Ethics Committee at Tohoku University School of Medicine.

Total RNA extraction from endometrial tissues and cDNA synthesis. All tumor and normal specimens were frozen in liquid nitrogen and stored at –80°C. Total RNA was extracted from normal endometrium and carcinoma tissues, using the RNeasy kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. A reverse transcription kit, SuperScript III RT (Invitrogen, Carlsbad, CA, USA), was used for the synthesis of cDNA.

Real-time reverse transcription–polymerase chain reaction (RT-PCR). Real-time PCR was carried out using the LightCycler System (Roche Diagnostics, Mannheim, Germany). cDNAs of known concentrations for target genes and the housekeeping gene, ribosomal protein L13a (RPL13A) were used to generate standard curves for determining the quantity of target cDNA transcripts. The mRNA level in each case was represented as a ratio with RPL13A.[23] The PCR thermal profile for MK was: initial denaturation at 95°C for 10 min followed by 32 amplification cycles of denaturation at 95°C for 10 s, annealing at 68°C for 10 s, and elongation at 72°C for 12 s; and for RPL13A, initial denaturation at 95°C for 10 min followed by 30 amplification cycles of denaturation at 95°C for 12 s, annealing at 68°C for 10 s, and elongation at 72°C for 12 s.

The primer sequences used in our study were: 5′-CCA AGA CCA AAG CAA AGG-3 and 5′-GGC AGG GCA TGA TTG ATT-3′ for MK; 5′-CCT GGA GGA GAA GAG GAA AGA GA-3′ and 5′-TTG AGG ACC TCT GTG TAT TTG TCA A-3′ for RPL13A.

Immunohistochemistry. After deparaffinization and rehydration in graded alcohol, antigen retrieval for MK immunostaining was done by heating the sections in a 600-W microwave for 20 min in 10 mM trisodium citrate buffer, pH 7.0. The sections were then blocked with normal goat serum for 30 min at room temperature, followed by incubation with chicken antihuman MK antibody (given by K.K.) overnight at 4°C. The dilution of the primary antibody used in this study was 1/250. The slides were incubated in 99.7% methanol containing 0.3% hydrogen peroxide at room temperature for 30 min to inhibit endogenous peroxidase. They were then incubated with biotin-conjugated rabbit antichicken IgG (ICN Pharmaceuticals, Aurora, OH, USA) at room temperature for 30 min, followed by incubation with peroxidase-conjugated streptavidin for 30 min at room temperature, using a Histofine Kit (Nichirei, Tokyo, Japan). The antigen-antibody complex was visualized with a 3, 3′-diaminobenzidine solution (1 mmol/L 3, 3′-diaminobenzidine, 50 mmol/L Tris-HCl [pH 7.6], 0.006% H_2O_2) and counter-stained with hematoxylin. Serous adenocarcinoma of the ovary was employed as a positive control for MK immunostaining.[13] The primary antibody was replaced with phosphate-buffered saline (PBS) as a negative control. Samples were considered negative if none of the cells stained for MK. Very weak positive was defined as less than 5% staining, weak positive as 5–25% staining, moderate positive as 25–50% staining, and strong positive as more than 50% staining. Slides were then numerically scored based on immunoreactivity. A score of 0 was negative, 1 very weak, 2 weak, 3 moderate, and 4 strong positive.

ELISA for human MK. An ELISA for human MK was performed as described previously.[22] Briefly, human MK was produced using Pichia pastoris GS115 by transfection with a human MK expression vector, which was constructed into pHIL-D4 (Invitrogen). This yeast-produced human MK was used to immunize rabbits and chickens to raise antibodies. The rabbit antihuman MK antibody (50 mL of 5.5 mg/mL in 50 mM Tris HCl [pH 8.2], 0.15 M NaCl, 0.1% NaN_3) was coated onto the wells of microtiter plates (Polysorpplates; Nunc, Rochester, NY, USA) for 20 h at room temperature. After washing with 0.05% Tween 20 in PBS, the wells were blocked with 300 mL of 0.1% casein, 0.01% Microcide I (aMReSCO) in PBS for 20 h at 37°C. Plasma samples (10 mL each) were mixed with 100 mL of 50 mM Tris HCl (pH 8.4), 0.5 M KCl, 0.1% casein, 0.5% bovine serum albumin, 0.01% Microcide I, and 0.1 mg/mL peroxidase-labeled chicken antihuman MK antibody. Aliquots of 50 mL of this mixture were added to wells prepared as described above, and subjected to chromogenic detection at OD450 using tetramethylbenzidine as the substrate. This ELISA system shows linearity from 0 to 4 ng/mL of MK, and there is no crossreaction with Pleiotrophin.[22]

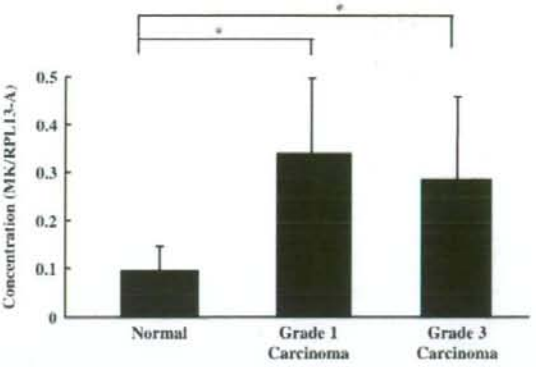

Fig. 1. Midkine (MK) mRNA expression levels in normal endometrial tissues and endometrial carcinoma tissues measured by reverse transcription–polymerase chain reaction (RT-PCR). MK mRNA expression levels in carcinoma tissues were significantly higher than in normal endometrial tissues ($P < 0.001$, Mann–Whitney test).

Statistical analysis. mRNA levels and serum concentrations of MK were compared using the Mann–Whitney test. Immunoreactivities for MK were compared using a Student's *t*-test. *P*-values less than 0.05 were considered significant.

Results

MK was expressed at higher levels in endometrioid adenocarcinoma tissues than in normal endometrium samples. To validate the microarray-based MK expression difference, we performed real-time RT-PCR using cDNA from 10 normal endometrium specimens and 20 carcinoma specimens: 10 were grade 1 and 10 were grade 3. The quantitative mRNA expression levels of MK were significantly higher in the endometrioid adenocarcinomas than in normal endometrium samples. However, there was no difference in the expression level between grade 1 and grade 3 (Fig. 1).

We then confirmed the high expression of MK in carcinoma tissues not only at the mRNA level but also at the protein level by immunohistochemical staining. The intensity of MK immunostaining in tissues is summarized in Table 1. As shown in Figure 2, MK protein was predominantly expressed in the epithelial cytoplasm with little nuclear expression. Positive staining for MK was scarcely detected in the stroma. In both normal proliferative and secretory phase endometrium samples, MK expression in the basal layer was significantly stronger than in the functional layer or endometrial stroma ($P < 0.001$, *t*-test) (Table 1 and Fig. 2c–f). No significant difference in protein expression was detected between the endometrial stroma and the functional layer in either the proliferative or the secretory phase. MK immunoreactivity at the basal layer tended to be stronger in

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Table 1. Midkine protein expression in normal and endometrial cancer tissues by immunohistochemistry (mean ± SD of immunostaining score)

Normal	*n*	Endometrial stroma	Functionalis	Basalis	
Total	33	0.41 ± 0.56	0.62 ± 0.89	*1.72 ± 1.17*	*P* < 0.001*
Proliferative	21	0.35 ± 0.61	0.62 ± 0.86	1.35 ± 1.18	
Secretory	12	0.50 ± 0.52	0.67 ± 0.98	2.17 ± 0.94	
Carcinoma	*n*	Endometrial stroma	Superficial area	Invasive area	
Total	85	0.38 ± 0.56	0.81 ± 0.78	*2.66 ± 0.79*	
G1	37	0.41 ± 0.55	1.00 ± 0.77	2.69 ± 0.82	
G2	25	0.32 ± 0.56	0.60 ± 0.71	2.56 ± 0.77	
G3	23	0.39 ± 0.58	0.75 ± 0.79	2.74 ± 0.81	

*P-value, *t*-test.

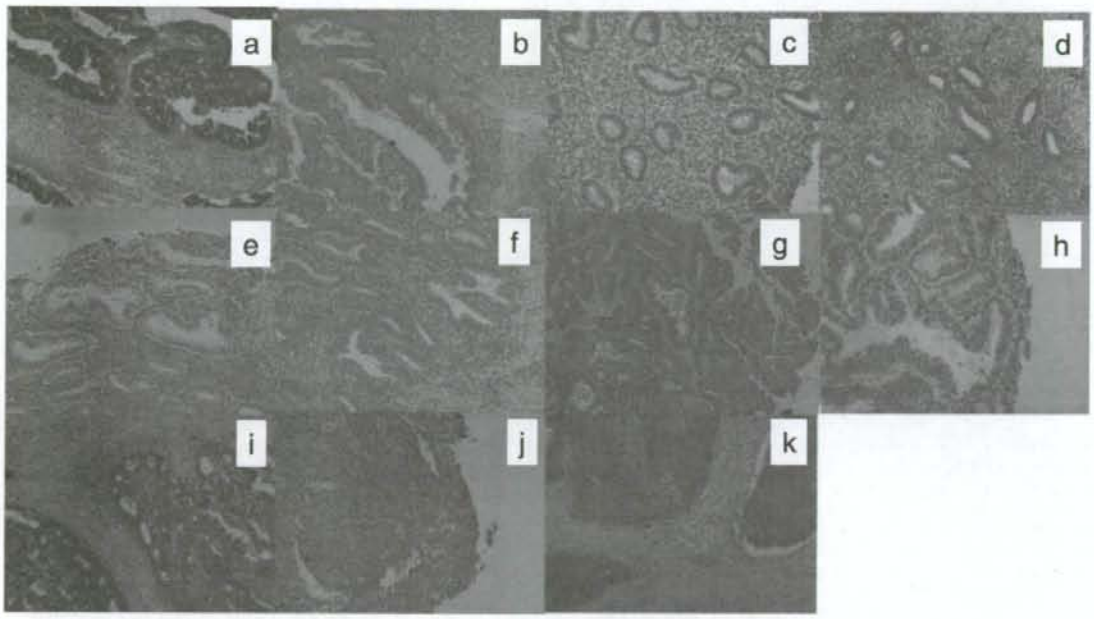

Fig. 2. Representative panels of immunohistochemical staining with anti-midkine (MK) protein antibody. (a) Positive control, (b) negative control, (c) proliferative phase (functionalis), (d) proliferative phase (basalis), (e) secretory phase (functionalis), (f) secretory phase (basalis), (g) transitional area of endometrial carcinoma grade 1, (h) superficial area of endometrial carcinoma grade 1, (i) invasive area of endometrial carcinoma grade 1, (j) superficial area of endometrial carcinoma grade3, (k) invasive area of endometrial carcinoma grade 3.

the secretory phase than in the proliferative phase ($P = 0.09$, *t*-test). Interestingly, MK expression was strongest at the margins of invasion and low in the superficial layers of the tumor samples (Fig. 2g–j). MK expression was significantly higher in the carcinomas than in the basal area of the normal endometrium ($P < 0.001$, *t*-test) (Table 1). No statistical correlation was detected between grade 1 and grade 3 endometrioid adenocarcinoma. MK immunoreactivity was not associated with any clinicopathological features including histological grade, depth of myometrial invasion, the presence of lymph node metastasis, or prognosis.

Serum MK protein concentration was higher in patients with endometrial carcinoma than in patients with benign gynecologic diseases. We measured serum MK protein concentrations with ELISA. Serum MK values for the patients with endometrial carcinoma was significantly higher than those for patients with benign gynecologic diseases ($P = 0.01$, Mann–Whitney test). The data suggest that MK protein is not only expressed in cancer tissues but also secreted into the sera at higher levels in endometrial carcinoma patients. To test whether the serum MK level could be used to discriminate endometrial carcinoma from benign disease, we set various cut-off values and classified the cases based on their MK values. Serum MK level had a high false negative ratio, thereby limiting its use in clinical applications.

A higher serum MK protein concentration was correlated with the presence of lymph node metastases and prognosis of endometrial carcinomas. We calculated the mean serum MK concentrations of cancer patients categorized by clinicopathological features. Results of the associations between clinicopathological parameters and serum MK levels are summarized in Table 2. Serum MK concentration was not associated with age, histological grade, or lymphovascular invasion. Although serum MK had a tendency to be lower in stage I–II or no myometrial

Table 2. Serum midkine (MK) levels and clinicopathological factors in endometrial carcinomas

Clinicopathological factors		N (%)	MK concentrations (Mean ± SD)	P*-values
Age	50 =	25 (21)	104 ± 253	0.111
	50 <	95 (79)	81 ± 113	
Histological grade	Grade1	66 (55)	82 ± 169	0.455
	Grade2	16 (13)	64 ± 97	
	Grade3	12 (10)	144 ± 112	
	Others	26 (22)	76 ± 143	
Stage	I–II	91 (76)	71 ± 157	0.054
	III–IV	29 (24)	133 ± 159	
Myometrial invasion	None	19 (16)	46 ± 76	0.074
	< 1/2	58 (48)	79 ± 178	
	= 1/2	40 (33)	100 ± 130	
	Unknown	5 (4)	183 ± 201	
Lymphovascular invasion	Negative	83 (69)	75 ± 153	0.720
	Positive	35 (29)	90 ± 139	
	Unknown	2 (2)	400 ± 33	
Lymph node metastasis	Negative	103 (86)	73 ± 142	0.008
	Positive	5 (4)	253 ± 246	
	Unknown	12 (10)	131 ± 161	
Prognosis	Non-recurrence	102 (85)	71 ± 142	0.009
	Recurrence or death	18 (15)	172 ± 184	

*P-value, Mann–Whitney test.

invasion, the difference was not statistically significant ($P = 0.054$, $P = 0.072$). Interestingly, the patient group with positive lymph node metastasis had a higher level of serum MK ($P = 0.008$, Mann–Whitney test). Patients with recurrence or cancer related death had significantly higher serum levels of MK protein than those without recurrence ($P = 0.009$).

Discussion

This is the first report showing that mRNA levels and protein expression of MK in endometrial carcinoma are significantly higher than in normal endometrium. Additionally, serum MK levels in endometrial carcinoma patients were significantly elevated relative to levels in patients with benign gynecologic diseases. Although MK is overexpressed in various human malignant tumors, its effects on tumor growth and progression are not fully understood. Growth of mouse colorectal carcinoma cells is inhibited by antisense midkine oligo DNA.[24] Transfection of the breast carcinoma line MCF-7 with MK accelerates tumor growth and increases tumor vascularity after cell implantation in nude mice.[25] MK also rescues Wilms' tumor cells from cisplatin-induced apoptosis.[26] These effects are likely mediated by signaling via phosphatidylinositol-3-kinase and mitogen-activated kinase.[27] Taken together these biological data support the hypothesis that MK plays an important role in oncogenesis and tumor progression.

Despite the increased MK immunoreactivity in endometrial carcinomas, there was no relationship between immunoreactivity and clinicopathological features. This was surprising since high MK immunoreactivity significantly correlates with worse clinical outcome of neuroblastomas,[17] urinary bladder cancer,[14] gastrointestinal stromal tumor,[28] oral squamous cell carcinomas,[29] and pancreatic cancer.[30] Interestingly, in esophageal carcinoma, MK is more intensely expressed in well-differentiated tumors than in poorly differentiated tumors.[11] A noteworthy immunohistochemical finding in this study was that the intensity of MK protein expression was not the same across different areas within a single tissue sample. MK expression in normal endometrium was higher in the basalis than in the functionalis. It was highly expressed at the margin of invasion but not in the superficial areas of the cancer specimens. To confirm that these findings were not due to the unequal localization of antibody, endometrial biopsy samples from cancer patients were also immunostained. These superficial specimens all demonstrated weak expression (data not shown). The MK immunohistochemical findings in normal endometrium were inconsistent with the previously reported pathophysiological effects of MK. MK is involved in angiogenesis and antiapoptosis. Microvessel density in normal endometrium, however, is not significantly different between the functionalis and basalis,[31] and apoptotic cells are equally distributed on each layer.[32] Donoghue *et al.* reported that lymphatic vessel density (LVD) is higher in the basalis than in the functionalis across the menstrual cycle.[33] In this study, the distribution of lymphatic vessels is consistent with the diversity of MK immunoreactivity across the menstrual cycle. Rogers *et al.* suggested that unknown lymphangiogenic growth factors may be involved in normal endometrium, since no difference is observed in immunostaining intensity for the vascular endothelial growth factor (VEGF)-C or VEGF-D between the functionalis and basalis.[33] We speculate that MK would be a candidate molecule for lymphangiogenesis in normal endometrium. In endometrial adenocarcinoma, the peritumoral LVD is higher compared with the LVD within the tumor and in normal endometrium, which also correspond to MK immunoreactivity. These observations suggest a role for MK in lymphangiogenesis in endometrial adenocarcinoma.

Since MK is a secretory protein, it could potentially be used to screen for and monitor the progression of endometrial carcinoma in a manner similar to cancer antigen (CA)–125 for ovarian cancer. An elevated serum MK level is detected in more than 80% of human adult carcinomas, and its level decreases when the tumor is resected.[19] A high serum MK level is associated with higher stage and disease progression in gastric cancer,[21] with tumor size in esophageal cancer,[20] and with progression in neuroblastoma.[22] As shown in Figure 3, serum MK was significantly elevated in patients with endometrial carcinoma compared with patients with non-malignant gynecologic diseases ($P = 0.014$). Regarding the relationship between serum MK concentration and clinicopathological features in patients with endometrial carcinoma, statistical differences were seen in both lymph node metastasis and prognosis. Our observations are consistent with another recent study in esophageal carcinoma.[34] In

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