同時併用化学放射線療法などが開発されてきた。特に頭頸部腫瘍における加速多分割照射は成果を上げ、治療成績の向上に寄与してきた。放射線生物学的因子を考える上では（1）腫瘍細胞自身の放射線感受性と、（2）腫瘍組織内の変化（腫瘍再増殖、腫瘍再酸素化）の両面から考える必要がある。腫瘍細胞の放射線感受性に関しては照射後のアポトーシス出現率との正の相関が報告されている。また種々の遺伝子発現（p53,bcl-2など）とアポトーシス出現頻度との正・負の相関も数多く報告されている。近年、DNA損傷修復蛋白（Ku70, Ku80など）の発現程度との相関も子宮頸癌などで報告されつつある[5]。通常これらの因子は病理組織学的検討によるため、画像化により放射線治療計画に利用できればさらに効果的な治療法の開発が期待できる。(2)においては腫瘍内の酸素濃度や低酸素細胞の存在が照射効果に影響を与えることはよく知られている（低酸素環境下では放射線抵抗性）。画像的にみると放射線開始後早期のMRIによるperfusion所見が治療効果と相関しており（**図2**）、組織内の再酸素化に依存していると考えられる[6]。また照射期間中の細胞増殖分画の変動や加速再増殖などが局所制御や生存率に関連があることが明らかになった。腫瘍組織への照射後に一時的に細胞増殖分画が増加することが報告され[7]、臨床においても放射線治療開始後早期においても確認されている[8]。

通常分割照射の場合、治療経過中の治療効果判定は40Gy前後（4週後）に行われることが一般的であるが、より早期に治療効果判定の予測がつけば治療方針の決定、たとえば化学放射線療法を継続するか手術療法に移行するか等の判断が速やかに行える。子宮頸癌では照射開始1週後の病理組織において、細胞周期における増殖分画の割合が増加した群で予後が良好であったと報告している。これは治療開始早期における放射線感受性の高い周期への再分布（recruitment）を見たものであると考えられている。このように照射開始後早期においては必ずしも腫瘍の死滅程度だけが局所制御率や予後に相関するわけではないので注意を要する。いずれにしてもこの時期におけるFDG-PETを中心とした機能画像により腫瘍の動態を把握できれば、治療方針の決定や放射線治療方法の工夫に大いに役立つと考えられる。

現在普及しつつあるCTやMRI画像を基にした3次元治療計画によるIMRTにおいては投与線量増加が可能となるため、当然局所制御率の向上が見込まれる。このため標的病変に放射線を集中させる工夫や位置精度の向上に関心が向けられてきた。しかし進行癌など多くの場合、定位照射のような極端な線量増加ができないため、さらなる治療成績の向上を図るには生物学的因子を加味した照射方法の工夫が求められている。

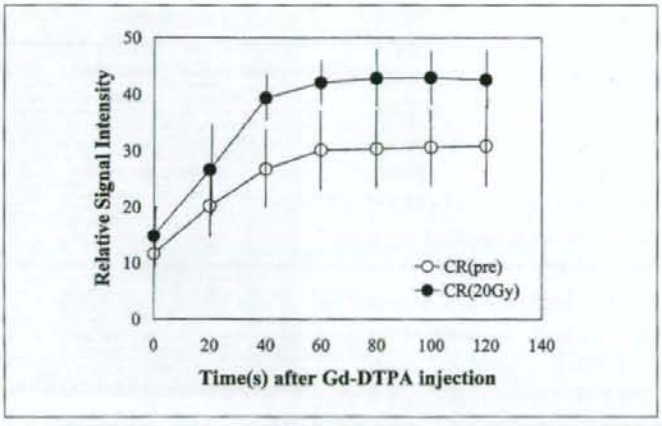

図2. 頭頸部癌患者に対する放射線治療中のMRI perfusion studyによる評価。
放射線治療後にCRとなった照射効果が良好な群では、20Gy時点で治療前に比べperfusionの増加が認められる[6]。

バイオイメージングと高精度放射線治療

近年のPET画像検査は細胞内の代謝能を視覚化する点において目覚しい発展を遂げている。さらにPET/CT検査においてはCTとの組み合わせでさらに診断精度が増しており、放射線治療計画にも用いられ始めている[9]。FDG-PETの有用性は多岐にわたり(1)病期決定、(2)放射線治療計画時の標的の決定、(3)治療効果判定、(4)予後予測などが挙げられる。現在、実際の臨床で放射線治療にFDG-PETが用いられているのは(1)、(2)の観点からである。化学放射線療法が普及してきた食道癌においてはリンパ節転移の有無の同定が他のモダリティーに比べ容易であり、照射野範囲の決定に重要な役割を果たしている[10]。肺癌では無気肺を伴う場合の肉眼的標的体積の決定や縦隔リンパ節転移の同定に有用である。照射野の設定に際してCTのみの場合とPET/CTを比較したところ、PET情報を加味することでGTVを縮小でき医師間でのばらつきが減じるという報告がなされており[11][12]、PET/CTは治療計画において重要な役割を担うことになると考えられる。切除不能非小細胞肺癌では化学放射線療法が標準治療であり照射は一般的に60Gyが用いられるが、近年さらなる局所制御ならびに治療成績の向上を目指し欧米で予防的照射領域を省き、画像で腫大が明らかな腫瘍病巣に対して3次元的な照射法を用いての線量増加試験が行われている。今後さらにがん細胞が真に存在する病巣の正確な同定が重要となる。肺癌においてはPET/CTがCTに比べ敏感度、特異度ともに良好であるという報告が多い。さらにそのPET/CT所見に基づく治療計画を行った放射線治療後の再発パターンの検討では照射野外の領域リンパ節再発の頻度は低率であったと報告されている[13]。今後、治療計画においてPET画像は必須のものとなると考えられる。

FDG-PETは優れた診断能以外に治療効果判定や治療効果予測にも有用であると報告されている。特に放射線治療開始後早期のSUV値と治療効果の間に相関があると述べているが[14]、治療早期に効果予測が可能となれば治療方針の決定(例えば放射線治療継続か手術へ移行するか等)に大いに役立つ。前項でも述べたように治療開始早期に治療効果や予後予測が可能となれば、治療方針の決定がより容易になる。通常40Gy前後になっての効果判定のため、判定中にいったん照射を休止してしまうと特に扁平上皮癌については治療効果の低下がみられることから、より早期に判定することが望ましい。

FDGは糖代謝に依存し通常酸素環境下で細胞分裂旺盛な細胞に集積するが、近年、アミノ酸代謝イメージングにメチオニン、また細胞増殖評価目的でフルオロチミジン(FLT)を用いたPET検査も開発されつつある。

放射線抵抗性である低酸素細胞集団の画像化も近年試みられ[15]、18F標識のニトロイミダゾール誘導体であるFMISO(fluoromisonidazole)やCu-ATSMの開発が進行中である。特に後者の集積機序はFDGと異なり低酸素環境下で細胞分裂が停止している領域に対してであり、今後期待される薬剤である。放射線治療、特にIMRTにおいてはブースト照射の治療計画において有用であると考えられる。低酸素細胞は放射線抵抗性であることから局所再発の大きな要因となっているため、その部分に対し追加ブースト照射を選択に行うことが可能となれば治療成績の向上に結びつく可能性があると考えられる。

細胞内の代謝能に加えがん細胞自体の特徴、すなわち細胞の蛋白や遺伝子発現まで可視化しようという試みも行われ始め、分子イメージングも現実のものとなろうとしている。腫瘍内の細胞動態や放射線抵抗性部分の局在が生物学的画像で把握できれば、IMRTのような腫瘍内の線量強度を変えて行うことでより効果的でかつ有害事象をおさえた放射線治療が可能となる。そのためには腫瘍の活動度や正常組織の機能を可視化することが求められる[12]。

アポトーシスの画像化も試みられている[16]。照射後のアポトーシス出現率と照射効果の相関はin vitroやin vivoの実験結果で明らかにされており、一般に照射効果が良好な腫瘍においてはアポトーシス出現率が高い。照射期間中の早期におけるアポトーシスの出現頻度は局所制御率予測に有用な可能性がある。ただし固形がんでは基本的にアポトーシスの出現率は高くなくin vitroの結果が臨床にそのまま使えるわけではないことを念頭に置く必要がある。

イメージベースの小線源治療

小線源治療は腫瘍に線量を集中させる治療手段として古くから用いられており、子宮頸癌に対しては腔内照射が重要な役割を担っている。子宮頸癌は進行癌であっても腫瘍に対して腔内照射で十分な線量が投与できれば、外照射との併用で局所制御可能な疾患である。現在の腔内照射は標準化された優れた治療法であるが、この際に線量投与の基本となったのがA点、B点という解剖学的位置座標である。国内では高線量率腔内照射は標準治療が確立し、病期による線量配分は配慮されているが、これらの点を指標に治療計画を行うため、腫瘍サイズや腫瘍の形状には配慮がなされていない。それでも良好な治療成績を得ていることから、外照射と腔内照射の組み合わせ方や線量配分や分割法の面において優れた治療法であるといえる。欧米においても従来はA点線量を基準にしていることには変りなかった。子宮頸癌の診断においてはMRI検査を中心に形状・進展範囲を詳細に検討している中、欧州を中心に腔内照射の見直しが行われ始めており、近年、GEC-ESTROでMRI画像を元にした子宮頸部の腫瘍の形状を基に標的を規定し、それに対する推奨線量を決め腔内照射を行う方向に急速に変わりつつある[17]。今後さらに低酸素細胞の局在分布など生物学的パラメーターを組み込んだ画像診断による評価が可能となれば、さらに最適な線量分布を目指した治療計画が可能となると考えられる。子宮頸癌は扁平上皮癌が主であり、低酸素による影響や細胞動態、遺伝子発現と予後との関連が多く報告されている領域であり、今後の画像診断の進歩が治療計画に反映されればさらに治療成績の向上が期待できる領域である。また前立腺癌においても小線源治療は重要な役割を占めているが、前立腺内の腫瘍の局在範囲が詳細にわかれば、線源を集中的に配置することが可能となるため、今後さらなるマクロ病理レベルの画像診断精度が治療計画に求められるようになると考えられる。

結語

放射線治療は局所療法であり、局所の詳細な画像診断が治療計画を行ううえで極めて重要である。単に病変の形状だけでなく腫瘍細胞自体の活動度や腫瘍の置かれている環境の評価が容易に画像を介して可能となれば、より精度が高精度な局所療法が実現すると考えられる。

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特集 高精度放射線治療における画像の役割

総 説

放射線治療計画における画像の役割①
定位放射線治療

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The role of diagnostic image in radiotherapy treatment planning①
Stereotactic radiotherapy

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要約

定位放射線治療（SRT）は脳転移などの頭蓋内の小病変（かつ少数）に対して、局所制御に優れた有効な治療法である。ガンマナイフなどの1回照射で治療を行う定位放射線手術（SRS）に比べ、直線加速器を用いたSRTは分割照射が可能であり有害事象の軽減が可能である。さらに腫瘍性病変に対しては分割照射が放射線生物学的に有利である。SRTは局所に限局した高精度治療であるため、腫瘍形状（GTV；Gross Tumor Volume）の正確な同定は極めて重要である。腫瘍の容積を過小評価すれば辺縁再発に直接結びつく。われわれはMRI用造影剤の倍量投与を行いGTVの確認を行っているが、腫瘍の形状や周辺組織との境界が明瞭となり治療計画において倍量投与は有用であると考えられる。

Abstract

Stereotactic radiotherapy (SRT) is effective for intracranial small tumor lesions including brain metastases. In comparison with stereotactic radiosurgery (SRS), as for hypofractionated SRT, the reduction of the adverse effects is enabled. The identification of GTV (Gross Tumor Volume) is extremely important in highly precise radiotherapy. We perform double-dose administration of contrast medium followed by identifying the GTV in MR images. By double-dose administration, the shape of the tumor and the border with normal tissue became clear. Therefore, we think double-dose administration of gadoteridol is very useful for treatment planning of highly precise SRT.

Key words 定位放射線治療、MRI造影剤、ガドテリドール、倍量投与、MRI、stereotactic radiotherapy、double-dose administration、gadoteridol、MRI

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はじめに

転移性脳腫瘍は無治療の場合予後が1ヶ月程度とされ、予後不良な病態である。放射線療法の標準治療は古くから全脳照射が確立されていたが、数々の報告でも全脳照射治療症例の平均生存期間は約2～7ヶ月程度[1]と、生存期間の延長は得られるものの、それでも予後不良な病態と言わざるを得ない。

Leksellによって提唱された定位放射線照射は極小照射野で線量を多方向から集中的に病巣局所に照射する治療法である。低侵襲ながら手術に匹敵する高い局所制御を得ることが可能とされており、直線加速器（ライナック）による治療も可能である。一般的に直径3cm以内で単発または少数（2～4個）の病巣に適応される。

RTOG（Radiation Therapy Oncology Group）は予後の改善が期待できる脳転移症例（PS良好、60歳未満、かつ原発巣が制御され、脳転移以外に転移病巣を認めない症例）において、これまでの全脳照射単独と比較して全脳照射＋定位放射線照射が局所制御率・PS（Performance Status）・QOL（Quality of Life）の向上、ならびに予後の延長について良好であったと報告している[1)2)3)]。予後の改善が期待できる単発または少数の転移性脳腫瘍症例について、全脳照射単独に定位照射を加えることにより、全脳照射単独よりも良好な治療成績を得ることが可能となった。現在では定位放射線照射は転移性脳腫瘍に対する標準治療のひとつに位置づけられている。

今回は当施設で行っている定位放射線治療（SRT：Stereotactic Radiotherapy）についての概説ならびに治療計画に用いるMRI造影剤倍量投与の有用性について述べる。

当施設における脳定位放射線治療の概略

当施設では直線加速器（リニアック）によるSRTを2003年度から行っている。直線加速器によるSRTは1998年4月1日に保険収載された。頭頸部へのSRTについては、照射中心の固定精度が2mm以内と定義され、頭頸部腫瘍（頭蓋内腫瘍を含む）、および脳動脈奇形に算定されている。われわれは治療計画装置にはBrain Scan（Brain Lab社製）を用い、照射時にはm3マイクロマルチリーフコリメータを用いて小照射野を規定している。

脳定位放射線治療のながれ

はじめにGaplessの1mmスライス厚造影MRIデータ収集を行う。この際に転移病変の個数を確認する必要がある。当施設では通常の診断用造影MRIは5mmスライス厚、1.5mm間隔で撮像を行っているが、この条件では微小な脳転移病変の場合、診断できないことがあるため注意が必要である。診断用造影MRIで単発または少数脳転移と判定されていてもSRT用MRIデータ収集にて多発脳転移が判明した症例は、この時点でSRTの適応から外れることになる。

つぎに非侵襲着脱式固定具の作成ならびに治療計画を行う。治療計画用のCT画像はMRI画像と違い、歪みのない情報が得られることから、CT画像を治療の座標系に用いる。治療計画CT撮像の際にローカライザーフレームを装着し、フレーム上のマーカーの位置を検出することにより定位座標空間の測定が可能となる。

定位用造影MRIデータと治療計画CTのデータをそれぞれ別個に治療計画装置（Brain Scan）に転送し、定位座標空間として用いる治療計画CTデータをローカライズしたのち、各々のデータ（CT・MRI）をソフトウエア（Brain Scan）上で融合させる。

CT、MRIの融合画像が矛盾しないことを軸位像、矢状断像、冠状断像でそれぞれ確認したうえで、造影MRI軸位像を用いて腫瘍の輪郭描画を行い、プラン作成を行う。GTV（Gross Tumor Volume）に2～3mmマージンをつけたものをPTV（planning target volume）とし、更にリーフマージンを2～3mmとって行っている。最終的にDVH（Dose Volume Histogram）を確認し、D95が投与線量の95%以上になるように設定している。

治療計画作成を行った後、SRTを行う前に位置精度確認を行う。ライナックによるSRTは固定具が着脱式であることから分割照射が可能である。少数分割照射は1回照射（定位放射線手術；SRS）と比べて急性期障害（一過性脳浮腫）ならびに晩期障害のリスクを軽減できるという利点があり、当施設では転移性脳腫瘍に対して3分割で定位照射を行っているが、治療時に再現性の精度確認を行う必要がある。位置精度確認は治療計画CTと同じ条件で固定具ならびにフレームを再装着して撮像したのち、CT画像上で適当な頭蓋内の基準点を選択し、基準点とフレーム上のマーカーの座標から

相対的な座標を算出したうえで、治療計画CTの時とずれがないかを確認する。位置精度は概ね1mm程度におさまっている。位置精度確認で2mm以上の大きなずれがないことを確認したうえで治療開始となる。

造影MRI倍量投与の有用性について

ガドテリドール（プロハンス®）は非イオン性マクロ管構造を持つMRI造影剤であり、倍量投与が保険適応となっている唯一の造影剤である。転移性脳腫瘍が疑われる患者に対して0.2ml/kgを静脈注射し、検出されないかまたは造影効果が不十分の場合、初回投与後30分以内に0.2ml/kgを追加投与することができる。

ガドテリドールを単量投与・倍量投与したSRT用造影MRI画像を次に示す。**図1**は単量投与・**図2**は倍量投与でそれぞれ同じスライス面を示している。症例は40歳代女性・乳癌脳転移の患者である。肉眼的に明らかに倍量投与のほうが濃染領域の範囲が拡がり、かつ正常組織との境界が明瞭になっているのが確認できる。**図3**は単量投与時の分布図で**図4**は倍量投与時の線量分布図を示している。濃染された領域に合わせて線量分布の範囲も異なっているのがわかる。

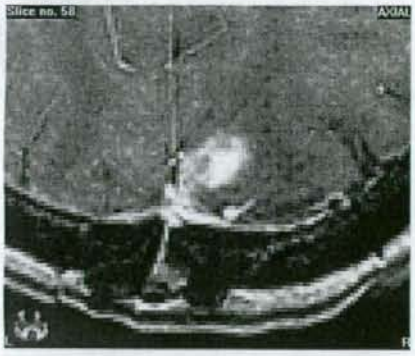

図1. 40歳代女性　乳癌術後脳転移（右後頭葉）
ガドテリドール単量投与のMRI T1強調画像である。

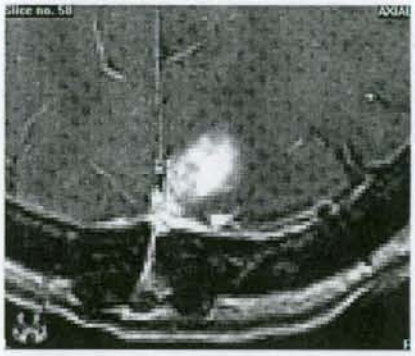

図2. ガドテリドール倍量投与を行ったMRI T1強調画像
図1.と同じスライス面を示している。単量投与よりも濃染範囲が拡大し周囲（正常組織）との境界は明瞭になっている。

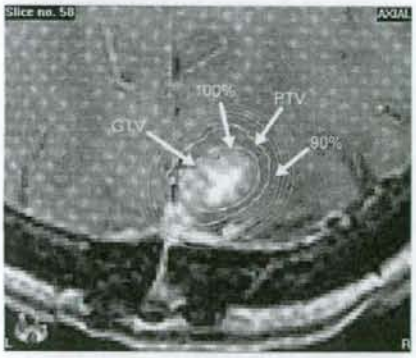

図3. ガドテリドール単量投与で治療計画作成を行った際の線量分布図（定位放射線治療）
腫瘍、PTVならびに投与線量の100%、90%ラインを表示している。

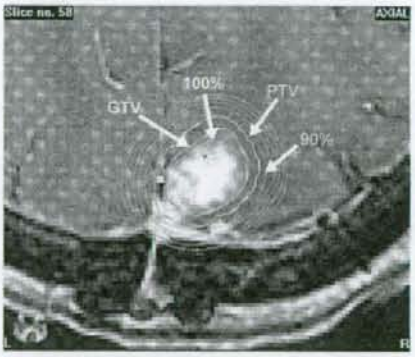

図4. ガドテリドール倍量投与で治療計画作成を行った際の線量分布図
図3.と比べて線量分布範囲が腫瘍の造影範囲に対して適切に設定されている。

症　例

急激な胸腔内再発・転移ならびに高カルシウム血症をきたし放射線抵抗性であった食道癌の一例

Aggressive intrathoracic metastases of radioresistant esophageal cancer with hypercalcemia

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Key Words : esophageal cancer, hypercalcemia, radioresistant

《はじめに》

悪性腫瘍に伴う高カルシウム血症は，悪性腫瘍が産生する液性因子[PTHrP；副甲状腺ホルモン関連蛋白（parathyroid hormone-related protein）]による腫瘍性体液因子性高Ca血症（HHM；humoral hypercalcemia of malignancy）と，骨局所での骨融解に伴うもの（LOH；local osteolytic hypercalcemia）があり，前者の頻度が圧倒的に高いとされる[1-2]。高カルシウム血症の臨床症状は多彩であり，腫瘍による悪液質の症状や化学療法・オピオイドなどの薬物療法による副作用との鑑別が困難な場合がある。今回われわれは，食道癌で術後早期に再発し，化学放射線療法等の積極的な加療を行ったにも関わらず，放射線治療照射野内を含めた早期再発および胸腔内転移・高カルシウム血症が進行した症例を経験したので若干の文献的考察を加え報告する。

《症　例》

患　者：60歳代男性

既往歴：高血圧，高脂血症

現病歴：胸部中部食道癌，臨床病期Ⅰ期（T1N0M0）の診断にて右開胸開腹食道亜全摘術が施行された。術前の食道内視鏡検査ではMt領域にⅠ型腫瘤性病変が認められた（図1）。術後病理診断は中分化型扁平上皮癌でありリンパ節転移は認められず，切除断端陰性で脈管侵襲は認められなかった。術後6か月後に右鎖骨上窩リンパ節腫脹が出現し，腫瘍摘出術にて食道癌のリンパ節転移と診断された。術後の化学放射線療法目的に当科入院となった。

身体所見：身長173cm，体重58kg（手術前体重70kg），右鎖骨上窩リンパ節腫脹を認めた。その他，特記すべきことなし。

入院時検査所見：血算は正常範囲以内であった。腎機能はCr 0.82mg/dlと正常で，Alb 3.7g/dl，Ca 8.7mg/bl（補正Ca値：9.0）であった。腫瘍マーカーは，SCC 0.8ng/ml，CEA 3.0ng/mlと基準値範囲内であった。

入院後経過：両側鎖骨上窩および縦隔リンパ節領域に対して，化学放射線療法を2コース施行した。放射線治療は，両側鎖骨上窩リンパ節領域な

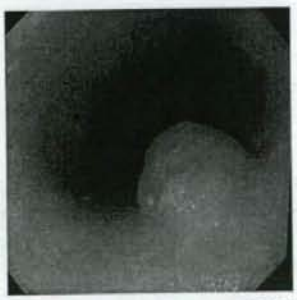

図1．食道内視鏡で胸部中部食道にⅠ型腫瘤性病変が認められた。

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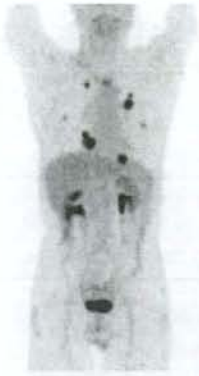

図2. PET/CT検査で多発性肺転移ならびに胸腔内播種が認められた。

らびに縦隔リンパ節(#107を含む)領域に対してT字照射にて開始した。40Gy/20回で脊髄を外し，腫瘍が残存している右鎖骨上リンパ節に照射野を絞り，計60Gy/30回の放射線治療を施行した。化学療法はlow dose FP療法(CDDP 10mg/body，5FU500mg/bodyそれぞれday1-5，8-12に投与，1コースを28日間とした)を2コース施行した。しかし治療終了時に胸部単純X線検査にて多発肺転移巣が疑われた。PET/CT検査を施行したところ，多発性肺転移ならびに胸腔内播種が認められた(図2)。PET/CT検査はFDG投与量3.7MBq/kg静注後にSiemens biograph 16にて撮像された。全身状態は良好で退院し，外来化学療法(Docetaxel 40mg/body，day1に投与，1コース14日間とした)を1コース施行した。その直後より呼吸困難，前胸部不快感や食欲不振が進行し，再入院となった。胸部CT検査では1カ月の間に急激な多発性胸腔内転移(多発肺転移，照射野内を含めた縦隔リンパ節転移，胸膜・心膜播種，胸水貯留)が認められた(図3a，b，c)。また，胸腔内転移の増悪とともに高カルシウム血症が進行した(図4)。骨シンチグラフィでは明らかな骨転移所見を認められず，intact PTH低値(5pg/ml：基準10-65pg/ml)，PTHrP高値(8pmol/l：基準0-1.1pmol/l)を呈していた。ビスホスフォネートによる治療を行ったが効果は不良であり，肺転移ならびに全身状態の急激な悪化を認め，再入院から1ヶ月後に死亡した。

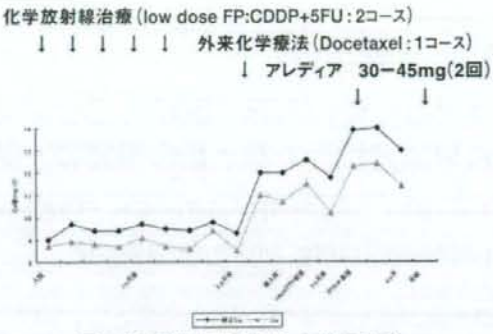

図4. 治療経過と血清カルシウム値の推移。

《考　察》

悪性腫瘍患者に高カルシウム血症が合併する頻度は施設によっても異なるが，約10～20%程度で多くは進行期にみられる[1]。終末期癌患者では2倍以上の頻度といわれている[2]。HHMを起こす悪性腫瘍は，扁平上皮癌(肺・皮膚・頭頸部)が最も多い[1]。機序としては扁平上皮癌からPTHrPが産生されると考えられている[3]。しかしHHMが悪性腫瘍の終末期になって突然生じる原因については解明されていない。本症例も手術時はI期食道癌であり，手術時の病理組織は中分化型扁平上皮癌であり，低分化や未分化の腫瘍細胞成分は認められなかった。にもかかわらず再発後は化学放射線療法中に肺転移をきたし，再発時は悪性度の高い病態と考えられた。

悪性高カルシウム血症発症後の予後は極めて不良であり[4]，井口らは高カルシウム血症の発現から大部分の患者は数ヶ月以内に死亡していると報告している[5]。Kuwanoらは手術を行った食道癌症例の7.7%の高カルシウム血症が認められ，予後不良因子であるとしている[6]。玉本らは病変が局所にとどまっている場合，放射線治療によりHHMが改善したと報告している[7]。辻仲はエルシトニンとシスプラチンの投与が有効であったと報告している[8]。しかし本症例においては高カルシウム血症に対してビスフォスフォネートを使用しても治療効果は不良であった。また化学療法はlow dose FP療法であったが治療直後に多発性肺転移が認められたことからも，シスプラチンに対する効果も不良と考えられた。さらに放射線治

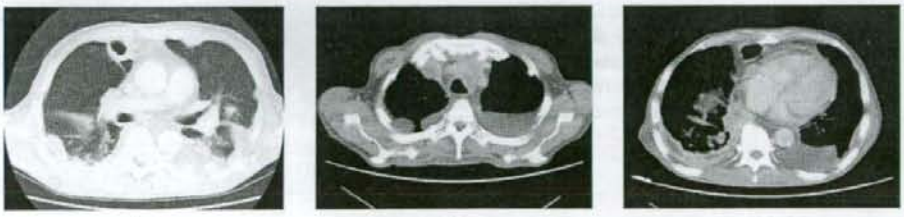

図3. 胸部CT検査で多発性肺転移(a)、上縦隔リンパ節転移(b)、胸膜播種病変(c)の急激な進行が認められた。

療後の照射野内病変は極めて早期に再増大が認められ，放射線抵抗性であった。

PTHrPを産生し急激な腫瘍進展を引き起こすに至る細胞悪性度の増加に加え，放射線抵抗性であることが本症例の特色である。

《結　語》

高カルシウム血症を伴い，急激な胸腔内再発・転移を生じ，放射線治療に抵抗性であった食道癌の一例を経験したので報告した。

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DISEASES OF THE COLON & RECTUM

ORIGINAL CONTRIBUTION

Preoperative Radiation Response Evaluated by 18-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival in Locally Advanced Rectal Cancer

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PURPOSE: This study focuses on the prognostic survival value of postirradiation metabolic activity in primary rectal cancer as measured with 18-fluorodeoxyglucose positron emission tomography.

METHODS: From July 1995 to March 2002, all 59 patients underwent two series of fluorodeoxyglucose positron emission tomography: one before preoperative radiation (standardized uptake values-1), and the other two to three weeks after radiation (standardized uptake values-2). Standardized uptake values-1 and standardized uptake values-2 correspond to before and after radiation, respectively.

RESULTS: In univariate analysis, the following emerged as significant prognostic variables: with or without residual tumor, pathologic differentiation, with or without recurrence, standardized uptake values-2, and with or without lymph node metastases. In multivariate analysis, residual tumor and standardized uptake values-2 were significant prognostic factors for survival. The median survival and the five-year overall survival rate comparing standardized uptake values-2 values <5 *vs.* >5 were 95 *vs.* 42 months and 70 *vs.* 44 percent, respectively (P=0.042).

CONCLUSION: A significant survival benefit was observed in patients with low fluorodeoxyglucose uptake after preoperative radiotherapy in primary tumors of rectal cancer.

KEY WORDS: Positron emission tomography; Radiotherapy; Prognostic value; Standardized uptake values; Rectal cancer; Preoperative radiation.

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A number of studies have reported that preoperative radiotherapy (RT) reduces the recurrence rate for locally advanced rectal cancer.[1–6]

Several studies have suggested that in selected patients with low rectal tumors, high-dose preoperative RT might permit the resection of the primary tumor with a high rate of preservation of sphincter function.[7–11] Such treatment results could have survival rates similar to those observed with more radical surgery without increasing the risk of pelvic or perineal recurrences.

However, except for a single European trial, definitive improvement in overall survival has not generally been demonstrated with preoperative RT alone.[5,12]

The prognosis of rectal cancer is generally related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement.[13–16] However, diagnostic accuracy of tumor penetration and nodal status is not sufficient.[17]

Many other prognostic markers have been evaluated retrospectively in determining the prognosis of patients with rectal cancer, although most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated.[18–20]

In those cases of rectal cancer in which preoperative RT was administered, nodal involvement and penetration of the tumor seemed to be significant for prognosis as well.[21–25] Besides nodal involvement and penetration status, no definitive prognostic markers have been reported in the preoperative radiation setting for this malignancy.

Prognostic information available before surgery is useful to select the candidates for a more aggressive surgical approach, such as extended lymphadenectomy, as well as intensive postoperative adjuvant therapy.[26–30] Also, the identification before the start of the entire treatment course of subsets of patients who are at low or high risk for recurrence can help to optimize treatment. For high-risk subsets, a more aggressive preoperative approach,

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such as combined modality preoperative treatment should be considered. Few predictors have been reported for this use.

Several studies have now been reported claiming the potential of fluorodeoxyglucose–positron emission tomography (FDG-PET) in predicting treatment outcome after preoperative RT for malignant neoplasms, including rectal cancer.[31,32] However, no consensus has been established on the usefulness of FDG-PET in predicting survival outcomes.

This study was designed to clarify the role of FDG-PET as a prognostic tool for patients with rectal cancer treated with preoperative RT.

PATIENTS AND METHODS

Study Design

From July 1995 to March 2002, the authors prospectively enrolled 59 patients with primary rectal cancer deemed eligible for preoperative RT, on the basis of a clinically bulky or tethered tumor or on imaging-based evidence of T3–4 or N1 disease by use of transrectal ultrasound. The distance from the anal edge of the tumor to the anal verge was <3 cm in 11 cases, 3 to 5 cm in 42 cases, and >5 cm in 6 cases. All patients received 50 Gy to the pelvis and were subjected to two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after radiotherapy ranged from 11–50; mean, 17; median 16). Surgery was performed 20 to 77 (mean, 43.3; median, 41) days after the completion of preoperative RT and 3 to 63 (mean, 26.2; median, 25) days after the second FDG-PET study.

The study was a prospective trial and had institutional review board approval. Informed consent was obtained from all patients.

Treatments

For RT, a 6-MV x-ray accelerator delivered 50 Gy in 25 fractions, 5 fractions per week during five weeks. Two AP/PA opposed fields were used as a Japanese conventional radiation technique for pelvic tumors. The clinical target volume included the entire pelvic cavity, anal canal, primary tumor, mesorectal and presacral lymph nodes, nodes along the internal iliac artery, lumbar nodes up to the level of the lower border of the fifth lumbar vertebra, and nodes at the obturator foramen. No chemotherapy was added to the RT in a preoperative setting. All surgeries were performed by colorectal specialists. Abdominoperineal resection with permanent colostomy was performed mainly for low rectal cancers located <5 cm from the anal verge, and for other rectal cancers mainly intersphincteric resection with coloanal anastomosis, according to surgeons' judgment. When residual tumor cells were found in the surgical resection margin, postoperative adjuvant 5-fluorouracil–based chemotherapy was performed.

Positron Emission Tomography, Standardized Uptake Values

All patients received two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after RT ranged from 11–50; mean days after RT, 17±7.6).[33] 18-fluorodeoxyglucose (18F) was synthesized using the Cypris Model 370 Cyclotron® (Sumitomo Heavy Industries, Shinagawa-ku, Tokyo, Japan), and FDG with an automated FDG synthesizer based on the method reported by Harms and Starling[11] radiochemical purity was >95 percent. The physical characteristics of this machine have been described in detail in a previous study.[31] Patients fasted for at least 4–1/2 hours before PET scanning so that serum glucose levels were between 80 and 110 mg/ml. All studies were performed using a Headtome IV dedicated PET scanner® (Shimadzu Corporation, Kyoto-city, Kyoto, Japan) with seven imaging planes at 13-mm intervals, each 10-mm thick. The inplane resolution was 4.5-mm full width at half maximum (FWHM). The axial resolution was 9.5-mm FWHM and the sensitivities were 14 and 24 kcps/(micro Ci/ml), respectively, for direct and cross planes. Each transmission scan was performed for eight minutes. For injections, 333 to 444 MBq of FDG were introduced via the cubital vein. A series of static acquisitions for 6 minutes each were initiated 60 minutes after the injection, and the mean time for the main tumor lesion was fixed at a constant setting of 63 minutes.

PET Data Analysis

Cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation. Image reconstruction was performed by using a filtered back-projection algorithm with a Hanning filter using a cutoff frequency of 0.3 and a 128×128 matrix. Several regions of interest (ROIs) were drawn manually on the hot spots of tumors. To minimize the partial volume effect associated with decreasing tumor sizes resulting from radiotherapy, the ROIs were set to have a number of pixels between 40 and 99. FDG accumulation was measured by using standardized uptake values (SUV) obtained by the following equation:

$$\text{SUV} = (\text{decay corrected PET value})/[(\text{injected dose})/(\text{body weight})].$$[33,34]

We defined SUVs in FDG-PET before preoperative RT as SUV_1 and two to three weeks after the treatment as SUV_2.

Pathologic Analysis

Analysis of the surgical specimen included a determination of the following parameters: 1) histologic type of the tumor; 2) degree of extension of the tumor through the rectal wall; 3) nodal involvement; and 4) status of proximal and distal margins. Pathologic response criteria were

Table 1. Univariate analysis

Factor	N	Relative risk	95% confidence interval	P value
Residual tumor				
+	8	1		
−	51	0.147	0.056–0.384	<0.0001
Differentiation				
Well	41	1		0.0011
Moderate	11	3.923	1.229–12.518	0.0210
Mucinous	4	6.14	1.57–24.012	0.0091
Poorly	2	23.093	4.09–130.371	0.0004
Unknown	1			
Recurrence				
+	31	1		
−	28	0.113	0.026–0.494	0.0038
Post-SUV	59	1.306	1.073–1.591	0.0079
SUV ratio				
>100%	4	1		
<100%	55	0.239	0.067–0.854	0.0276
LN				
+	30	1		
−	29	0.341	0.121–0.958	0.0411
Astler-Coller				
B1	10	0.21	0.027–1.63	0.1354
B2	18	0.315	0.088–1.132	0.0767
C1	4	1.123	0.247–5.097	0.8808
C2	26	1		0.1643
SUV ratio	59	1.014	0.994–1.033	0.1648
Pre-SUV	59	1.088	0.962–1.232	0.1788
Pathologic effect				
Grade 0	2	0.235	0.014–4.059	0.3193
Grade 1	44	0.102	0.012–0.868	0.0366
Grade 2	12	0.121	0.012–1.182	0.0693
Grade 3	1	1		0.1877
Sex				
Male	37	1		
Female	22	0.603	0.215–1.692	0.3363
Age (yr)	59	0.986	0.941–1.032	0.5392

SUV=standardized uptake values, LN=lymph node metastases.

defined as proposed by the Japanese Society for Esophageal Disease: Grade 0, no treatment effect; Grade 1, more than one-third viable tumor cells; Grade 2, less than one-third viable tumor cells; and Grade 3, no viable tumor cells.[35]

Statistical Analysis

Statistical analyses were performed by using StatView Dataset File version 5.0 J for Windows computers. Survival periods were calculated from the start of irradiation. The survival functions were estimated with the Kaplan-Meier method estimator, and log-rank tests were used to compare the survival distributions. Both univariate and multivariate analyses for survival were performed.

RESULTS

Pathologic effect and SUV ratio (SUV_2/SUV_1) were related statistically ($P=0.047$). Pathologic effect, however, showed no significant correlation with recurrence and survival. Histologic tumor type and SUV ratio were correlated and the ratio was >100 percent when the tumor type was poorly differentiated adenocarcinoma. Although recurrence rate tended to be higher with an elevated value of SUV_2, there was no significant association between them.

SUV ratio showed a tendency to be related with recurrence, and recurrence rate was of marginally higher significance when SUV ratio was >100 percent. Survival period was significantly short when SUV ratio was >100 percent ($P=0.0121$) and/or when SUV_2 was >5 ($P=0.0378$).

In univariate analysis, residual tumor, pathologic differentiation, recurrence, SUV_2 value, and lymph node metastasis were significant prognostic factors (Table 1). In multivariate analysis, no residual tumor and SUV_2 were significant prognostic factors for survival (Table 2). The survival curves comparing patients with *vs.* without residual tumor are shown in Fig. 1. Notably, when SUV_2 value was >5, overall survival was significantly poorer (Fig. 2). The median survival time and five-year overall survival rate comparing <5 *vs.* >5 SUV_2 value was 95.4 *vs.* 41.9 months and 70.4 *vs.* 43.6 percent, respectively ($P=0.042$).

DISCUSSION

SUV before RT and Prognosis

In this study, recurrence or poor prognosis was not related to high SUV before RT, which is in agreement with previously published reports. For head and neck cancers, Greven *et al.*[36] claimed that SUV before RT did not have any correlation with local control when examined for the entire group, primary site, or T stage (n=45). Others, however, have reported studies that differed from our results. Both Allal *et al.*[37] and Rege *et al.*[38] concluded that FDG uptake followed by RT, as measured by the SUV, had potential value in predicting local control and survival in head and neck carcinomas (n=63 and n=12, respectively).

SUV after RT and Prognosis

Recurrence or poor prognosis was related to high SUV after RT in our study. This result also concurs with earlier

Table 2. Multivariate analysis

Factor	Relative risk	95% confidence interval	P value
Residual tumor	0.302	0.094–0.973	0.0449
Differentiation			
Well			0.1552
Moderate	2.774	0.734–10.482	0.1326
Mucinous	2.875	0.574–14.406	0.1990
Poorly	10.486	0.988–111.283	0.0511
Recurrence	0.155	0.019–1.297	0.0854
Post-SUV	1.502	1.128–2	0.0054
SUV ratio <100%	0.675	0.107–4.268	0.6759
LN	0.362	0.080–1.637	0.1867

SUV=standardized uptake values; LN=lymph node metastases.

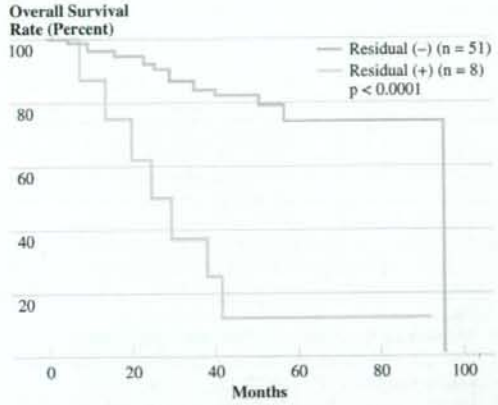


FIGURE 1. Overall survival curves comparing patients with *vs.* without residual tumor.

reports.[39,40] Higher SUV after preoperative RT predicts poor prognosis. Kunkel *et al.*[39] concluded that postirradiation FDG-uptake significantly predicted survival ($P=0.046$) and local tumor control ($P=0.0017$) in advanced oral squamous-cell carcinoma (n=35). Brun *et al.*[40] concluded that when a high initial tumor SUV was found, the reduction of SUV in the second PET examination might predict local tumor response in head and neck cancer (n=17). Swisher *et al.*[41] concluded that FDG-PET was predictive of survival in patients with esophageal carcinoma who had received preoperative chemoradiation ($P=0.01$; n=83). In our previous report,[32] only SUV_2 correlated with recurrence, although no significant correlation was observed in this study. It might be explained by the increased number of the patients involved to the study.

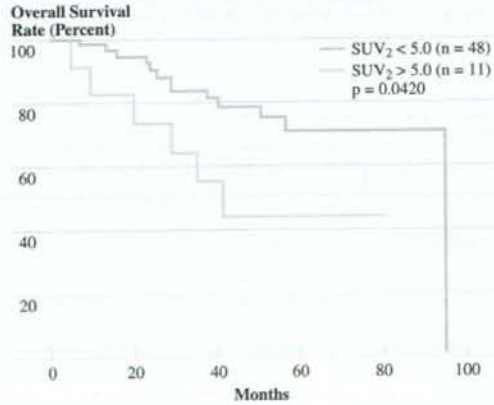
SUV before or after RT and Histologic Effects

SUV before or after RT was marginally correlated with histological effects. This finding is in agreement with previous reports. Kunkel *et al.*[42] reported a significant correlation ($P=0.045$) between post-RT FDG-uptake and histologic tumor regression was observed for mouth carcinoma (n=30). In their report, SUV > 2.75 as a practical clinical threshold value for the identification of residual tumor resulted in a specificity of 88 percent, sensitivity of 68 percent, a positive predictive value of 94 percent, and a negative predictive value of 50 percent (in their report]).[41,42] In our actual follow-up data, a significant correlation could not be confirmed between post-RT SUV and patients' survivals. Brücher *et al.*[43] claimed an association for histology and survival in esophageal squamous-cell carcinoma (n=24). In responders, FDG uptake decreased by 72±11 percent; in nonresponders, it decreased by only 42±22 percent. Nonresponders to PET scanning (n=11) had a significantly poorer survival after resection than responders. Flamen *et al.*[44] also reported a correlation with histology and survival in locally advanced esophageal cancer (n=36). Response to chemoradiation as assessed by serial FDG-PET was strongly correlated with pathologic response ($P=0.002$) and survival ($P=0.087$).[44] In our study, SUV value after preoperative RT (SUV2) was significant in overall survival. In addition, the SUV ratio (SUV2/SUV1) showed an association with histopathologic effects and recurrence. These values are only available after the completion of preoperative radiation. In this respect, they may influence the surgical approach and postoperative adjuvant therapy. For example, if SUV1 was a prognostic marker, decisions could be made regarding preoperative treatment. SUV1 can control the entire treatment strategy, whereas SUV2 defines the surgical procedure and postoperative adjuvant therapy.

FDG-PET for Prediction of Survival in Rectal Cancer

The important implication of this study is that FDG-PET may be useful in assessing cytotoxic or ablative therapy. de Geus-Oei *et al.*[45] reported that a significant benefit ($P=0.017$) was observed in patients with low FDG uptake (SUV < 4.26) with metastases of rectal cancer (of 152 patients, 67 were treated with resection of metastases and 85 with chemotherapy). A recent study from the Memorial Sloan-Kettering Cancer Center reported on monitoring the response to therapy with FDG-PET and the biologic basis of the change in FDG uptake of tumors in patients treated with neoadjuvant chemotherapy for hepatic colorectal metastases (13/42 evaluated patients underwent preoperative chemotherapy).[46] Fernandez *et al.*[47] concluded that post-resection screening by FDG-PET was associated with excellent five-year overall survival for patients undergoing resection of hepatic metastases from colorectal cancer (19 studies; 6,070 patients). Guillem *et al.*[48] from Memorial

FIGURE 2. Overall survival according to standardized uptake values-2 (SUV_2).



Sloan-Kettering Cancer Center suggested that FDG-PET might be useful in assessing the response of primary rectal cancer to chemoradiotherapy (n=15).

Denecke *et al.*[49] compared CT, MRI, and FDG-PET in the prediction of outcome of neoadjuvant radiochemotherapy in 23 patients with locally advanced primary T3/4 rectal cancer. The mean SUV reduction in responders (60±14 percent) was significantly higher than in nonresponders (37±31 percent; $P=0.03$). The sensitivity and specificity of FDG-PET in identifying response was 100 percent (CT 54 percent, MRI 71 percent) and 60 percent (CT 80 percent, MRT 67 percent). Positive and negative predictive values were 77 percent (CT 78 percent, MRI 83 percent) and 100 percent (CT 57 percent, MRI 50 percent) (PET $P=0.002$, CT $P=0.197$, MRI $P=0.5$). Additionally, Kalff *et al.*[50] evaluated the prognostic information obtained from the degree of change in tumor FDG-PET uptake induced by chemoradiation before radical curative surgery in 34 patients with T3/T4 rectal cancer. PET response was highly significantly associated with overall survival duration ($P<0.0001$) and time to progression ($P<0.0001$). Complete pathologic response was the only other statistically significant prognostic factor ($P<0.03$). The percentage of maximum SUV change after chemoradiation was not predictive of survival in partial metabolic response patients. Guillem *et al.*[31] tried to determine the prognostic significance of FDG-PET assessment of rectal cancer response to preoperative chemoradiation. The mean percentage decrease in SUV_{max} (ΔSUV_{max}) was 69 percent for patients free from recurrence and 37 percent for patients with recurrence ($P=0.004$). $\Delta SUV_{max} \geq 62.5$ was the best predictors of no-evidence-of-disease status and freedom from recurrence. Patients with $\Delta SUV_{max} \geq 62.5$ had significantly improved disease-specific and recurrence-free survival ($P=0.08$ and $P=0.03$, respectively).

The continued accumulation of clinical data on SUV for preoperative RT will contribute to establishing its usefulness. Studies in other malignancies, such as maxillary sinus carcinoma, are under consideration, for which preoperative RT is frequently performed.

CONCLUSION

A significant survival benefit was observed in patients with low FDG uptake (SUV<5) after preoperative radiotherapy in primary tumors of rectal cancer.

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MALT lymphoma

Radiotherapy for 41 patients with stages I and II MALT lymphoma: A retrospective study☆

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Abstract

***Purpose*: Mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct disease with specific clinical and pathologic features that may affect diverse organs. We analyzed our recent experience with Stage I/II MALT lymphoma presenting in the stomach and other organs to assess the outcome following radiation therapy (RT) alone.**

***Patients and methods*: Forty-one patients with Stages I (37) and II (4) disease were treated between 2000 and 2006. Patients with transformed MALT were excluded. The median age was 60 years (range, 25–86 years), male: female ratio 1:1. Presenting sites included stomach, 11; orbital adnexa, 21; thyroid, 1; other head and neck, 3; small bowel, 3; skin, 1; and rectum, 1. Thirty-five patients (85%) received RT-alone and 6 (15%) received antibiotics followed by RT. RT dose was 30 Gy in 20 fractions (fr) in all 41 patients. Mean follow-up time was 32.0 months (range, 2.1–162 months).**

***Results*: A first complete response was achieved in all 41 patients. Only one patient died from bile duct carcinoma at 22 months from the start of irradiation for conjunctiva MALT lymphoma without recurrence of lymphoma. The other 40 patients were alive. Thirty-eight patients out of them were alive without recurrence. One patient with a duodenal lymphoma had a recurrence in non-irradiated distant sites at 1 month. Another patient with a bilateral eye lid lymphoma had a recurrence within radiation field at 41 months. The absolute local control rate with radiation was 98% (40/41 patients).**

***Conclusion*: Localized MALT lymphomas have excellent prognosis following moderate-dose RT (30 Gy/20 fr).**
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Keywords: Non-Hodgkin's lymphoma; MALT; Treatment; Radiation therapy

Mucosa-associated lymphoid tissue (MALT) type lymphoma is now incorporated into the Revised European–American Lymphoma (REAL) and the World Health Organization (WHO) classification systems [1,2] as extranodal marginal zone B-cell lymphoma, MALT type. It accounts for 4–13% of patients seen in individual cancer centers [3,4]. A recent nationwide study of malignant lymphoma among Japanese reported that it accounts for about 8% of all malignant lymphomas in Japan [5]. Although much knowledge has been gained in defining the clinical features, natural history, pathology, and molecular genetics of the disease in the last decade, the optimal treatment approach for MALT lymphomas is still evolving. The discovery of an association between *Helicobacter pylori* (*H. pylori*) infection and gastric MALT lymphoma, and tumor response with eradication of *H. pylori* [6–10], led to the novel concept that MALT lymphoma can be cured with removal of the underlying antigenic stimulus, the *H. pylori* infection. Predisposing conditions to MALT lymphoma are well recognized: Hashimoto's thyroiditis for thyroid MALT lymphoma [11] and Sjögren's syndrome for salivary gland MALT lymphoma [12].

Because 60–70% of patients with MALT lymphomas present with localized (Stage I or II) disease [3,13,14], and because there is a tendency for the disease to remain localized for a long time, local treatment, such as radiotherapy (RT), is often indicated. Previous retrospective studies demonstrated excellent local control rates and progression-free survival (PFS) after RT [15–30]. RT for orbital MALT lymphomas usually leads to late adverse events such as retinopathy, cataracts, or a dry eye [15–24]. Furthermore, there have been few published prospective trials evaluating the appropriate dose and field of RT for MALT lymphoma, except for patients with localized gastric disease [29]. Japan Radiation Oncology Group (JAROG) conducted a multicenter phase II study to evaluate moderate-dose (30.6–39.6 Gy) of RT between 2002 and 2004, depending upon the primary site and tumor bulk [31]. They concluded that moderate-dose RT was highly effective in achieving local control with acceptable morbidity in 37 patients with MALT lymphoma.

☆ Clinical investigation lymphoma

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Over the last decade and a half, works on multiple MALT lymphoma treated with RT series were published, and many of these words were specific to the organ that was treated. The radiosensitivity of MALT to radiation is also well established and the dose of 30 Gy to the stomach and even lower doses to orbital MALT lymphoma are standard of care. However, to date there are few well-documented reports of the efficacy of RT in this disease. We report the analysis of our experience of 30 Gy/20 fr involved-field RT for Stages I and II MALT lymphomas, emphasizing the excellent local control with radiation.

Methods and materials

This is a retrospective study. Forty-one consecutive patients with Stages I (37) and II (4) disease were treated between 2000 and 2006 in our institution. Patients with transformed MALT were excluded. Additionally, primary nodal marginal zone B-cell lymphoma, MALT type ($N = 2$) was also excluded. The median age was 60 years (range, 25–86 years) and male/female ratio was 1/1. Presenting sites included stomach, 11; orbital adnexa, 21; thyroid, 1; other head and neck, 3; small bowel, 3; skin, 1; and rectum, 1 (Table 1). Staging included site-specific imaging, enhanced CT or MRI in 39 patients (95%), gallium-68 scintigraphy in 7 (17%), F-18 2-deoxy-fluoro-D-glucose (FDG) positron emission tomography (PET) in 20 (49%), and bone marrow biopsy in 39 (95%). The diagnosis was made on the basis of hematoxylin and eosin-stained biopsy specimens supported by immunohistochemical analysis. Immunologic phenotyping on paraffin section was done for κ and λ light chain restriction and $CD20^+$, $CD5^-$, $CD10^-$, and cyclin $D1^-$, which in the context of the microscopic appearance, is consistent with MALT lymphoma.

Table 1
Patient and tumor characteristics

	No.	%
Anatomic location		
Stomach	11	27
Orbital adnexa	21	51
Thyroid	1	2
Other head and neck	3	7
Small bowel	3	7
Skin	1	2
Rectum	1	2
Maximum diameter of tumor		
≧5 cm	20	49
<5 cm	21	51
Sex		
Male	21	51
Female	20	49
Age		
≧60	21	51
<60	20	49
Stage		
IE	34	83
IEE	3	7
IIE	4	10
K-PS		
≧90%	39	95
<90%	2	5

Radiation method

The clinical target volume (CTV) was defined as an entire affected organ for lymohoma of the stomach or gross tumor volume (GTV) with at least 20 mm of margin for lymohoma of the small bowell, thyroid, other head and neck, skin, and rectum. Prophylactic irradiation for lymph node was not performed. The CTV was defined as the entire bulbar and palpebral conjunctiva for the orbital lymphoma with lesions confined to the conjunctiva or eyelids. The CTV was the entire orbital cavity for the retrobulbar lymphoma. A lens shield was placed unless the block compromised tumor coverage. One example of radiation dose distribution for gastric MALT lymphoma was shown in Fig. 1. RT dose was 30 Gy in 20 fr in all 41 patients regardless of the size of primary tumor. In the gastric lymphoma patients, the liver and kidneys were evaluated as the organs at risk. Of the 21 patients with orbital MALT lymphoma, 14 patients were treated with a cylindrical lens shielding (approximately 6–12 mm thick, depending on the electron beam energy). Lens shielding was placed 1 cm above the cornea.

Systemic therapy

Helicobacter pylori status was determined by the rapid urease test (Helico Check, Otsuka Co., Tokushima, Japan), serological testing (HM-CAP kit, Enteric Product, Inc., NY, USA) and ^{13}C-urea breath test before and after *H. pylori* eradication therapy. Thirty-five patients (85%) received RT alone and 6 patients (15%) that were positive of *H. pylori* infection in gastric lymphoma received antibiotics followed by RT. When patients were refractory to antibiotics or their cases were not associated with *H. pylori*, they were candidates for RT for gastric MALT lymphoma. Accordingly, cases in which *H. pylori* were completely eradicated only by antibiotic treatment were not indicated for RT. The determination of a failed response to *H. pylori* eradication therapy has so far been made at 12 months after the therapy, and RT has been applied to patients who did not achieve complete remission at that time. Patients who had simultaneous bilateral lesions were classified with Stage IEE disease according to other investigators' criteria [32–36].

Quality of follow-up

After the completion of radiotherapy, patients were followed at regular intervals. Careful clinical and ophthalmologic examinations were performed every 1–3 months for the first 2 years, every 4–6 months through year 5, and annually thereafter. For the patients with gastrointestinal MALY lymphoma, endoscopic, CT scanning and histological evaluation were performed immediately after radiotherapy and every 3–6 months thereafter. For the patients with orbital MALT lymphoma, orbital CT scanning or magnetic resonance imaging was recommended at 1 year after

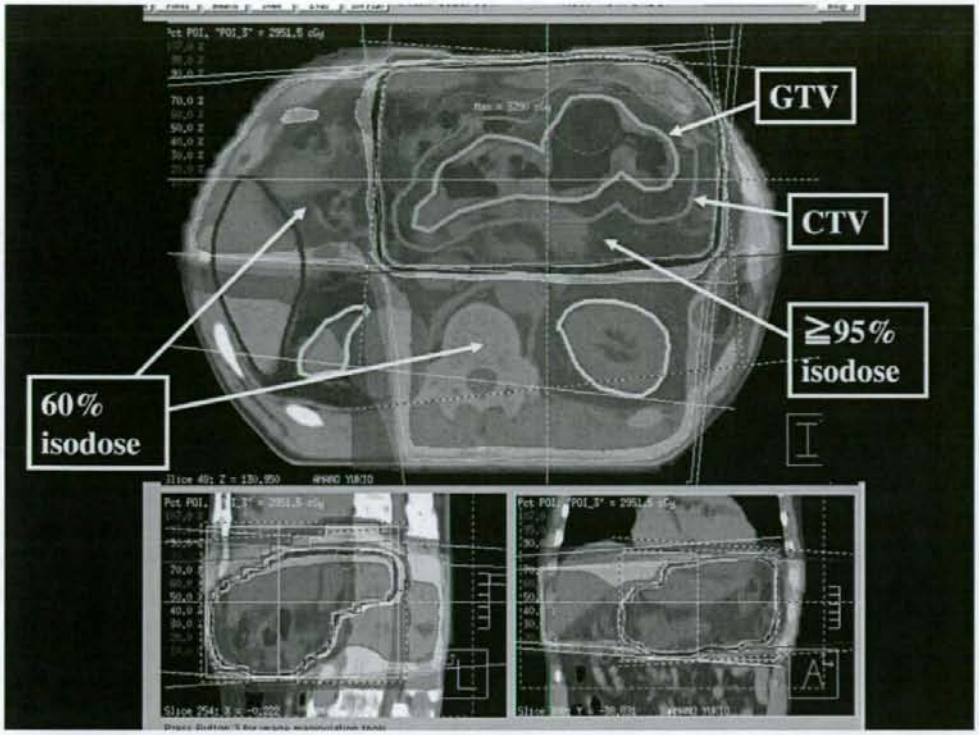

Fig. 1. Radiation dose distribution in the virtual simulation using a CT simulator of a gastric MALT lymphoma. The radiation portal consisted of a combination of the anterior–posterior direction and the lateral direction.

radiotherapy but was not required and other radiographic studies were performed as indicated clinically.

Statistical methods

The progression-free survival (PFS) was assessed using the method of Kaplan and Meier. Acute toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Late effects were graded according to the Radiation Therapy Oncology/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Results

A first complete response was achieved in all 41 patients. Only one patient died from bile duct carcinoma at 22 months from the start of irradiation for conjunctiva MALT lymphoma without recurrence of lymphoma. The other 40 patients were alive. The 5-year overall survival rate was 96.7%. Thirty-eight patients out of them were alive without recurrence. The absolute local control rate with radiation was 98% (40/41 patients). Progression-free survival (PFS) curve of the 41 patients is shown in Fig. 2. The 5-year PFS rate for the entire group was 90.6%. Mean follow-up time was 3.3 years (range, 0.2–12.2 years).

The PFS took into account not only local relapses but also distant relapses. One relapse (the primary site: duodenum) was observed in non-irradiated distant sites at 1 month. The

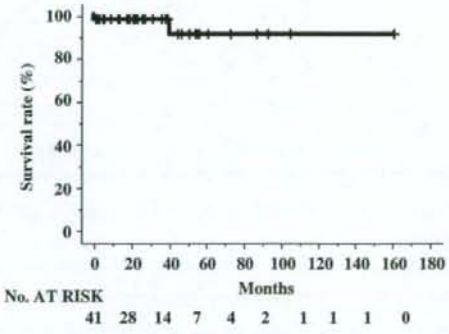

Fig. 2. Progression-free survival of the 41 patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

patient with a duodenal lymphoma had a recurrence in the abdominal para-aortic lymph node showing transformation into diffuse large B-cell lymphoma. After the recurrence, the patient was given systemic chemotherapy consisting of 6 cycles of R-CHOP regimen. It involved the monoclonal antibody rituximab, and the drugs: cyclophosphamide, doxorubicin, vincristine and prednisolone. After the salvage therapy, no recurrence has been detected until now for 71 months.

Another relapse (originated from bilateral eye lid) was within electron irradiation field at 41 months. The relapse lesion in the left lower eyelid was resected completely. The pathology remained unchanged. After the resection, no recurrence has been detected till now for 53 months (Table 2).

Acute toxicity and late complications

Radiation-induced side effects were negligible in the majority of the patients. No life-threatening toxicity (≥grade 4) occurred. Although acute radiation-induced conjunctivitis developed in 5 patients, none of them had severe later complications. The incidence of any later complications is listed in Tables 3 and 4. Cataract did not develop in any of the 14 patients who were treated with lens shielding. We observed three Grade 3 cataracts during this study period at 36, 46, and 162 months after the completion of RT.

Discussion

Because MALT lymphoma has been considered to be less responsive to standard chemotherapy than other aggressive lymphomas, RT has been used as the first line local treatment. Only for limited-stage gastric MALT lymphoma linking to *H. pylori* infection, *H. pylori* eradication therapy today has become recognized as a first-line treatment [50]. RT has been applied to patients who did not achieve complete remission after *H. pylori* eradication therapy.

This report on the RT treatment of MALT lymphoma in a variety of sites with involved-field RT of 30 Gy shows good clinical results. We have demonstrated that the PFS was 90.6% at 5 years. Our findings demonstrated that RT-alone was highly effective in achieving local control for localized MALT lymphoma. These favorable outcomes after RT are consistent with previous retrospective studies, which administered various doses of RT with a median of 25–40.5 Gy [15–24,26–30]. Many researchers concluded that 30 Gy of RT could achieve excellent local control.

Although several groups treating solely MALT lymphoma mentioned that 25–30 Gy is enough to control the disease [26,28], we also suggest that 30 Gy in 20 fr was appropriate for controlling MALT lymphoma without severe detrimental effects. Shu et al. [51] reported that the 10-year actuarial relapse-free survival, cause-specific survival, and overall survival rates were 93.1%, 97.9%, and 86.9%, respectively, for 48 orbital MALT lymphomas by RT of median 30.6 Gy (range; 5.4–30.6 Gy). Le et al. [52] reported 100% of the local control and recommended using a radiation dose of 30–30.6 Gy in 1.5–1.8 Gy fr for localized orbital MALT lymphoma. Zhou et al. [53] also reported 100% of the local control rate for orbital indolent lymphoma and concluded that a dose of 30 Gy was sufficient.

Table 2
Treatment and outcome characteristics

	No.	%
Radiation dose		
30 Gy/20 fr	41	100
Outcome		
Dead	1	2
Alive with recurrence	2	5
Alive without disease	38	93
The site of recurrence		
Within radiation field	1	2
Outside radiation field	1	2
Modality		
Electron	19	46
Photon	22	54
Energy		
6 MV	16	41
10 MV	6	15
6 MeV	18	44
12 MeV	1	2

Table 3
Acute and late toxicities in 21 orbital adnexa MALT lymphoma

	No. of patients (%)		
	Grade 0	Grades 1–2	Grade 3
Acute toxicities			
Dermatitis	18 (86%)	3 (14%)	0
Conjunctivitis/Corneitis	16 (76%)	5 (24%)	0
Total	13 (62%)	8 (38%)	0
Late toxicities			
Eyesight decline	19 (90%)	2 (10%)	0
Conjunctivitis/Corneitis	13 (62%)	8 (38%)	0
Cataract	16 (76%)	2 (10%)	3 (14%)
Total	7 (34%)	11 (52%)	3 (14%)

Table 4
Acute and late toxicities in 15 gastrointestinal MALT lymphoma

	No. of patients (%)		
	Grade 0	Grades 1–2	Grade 3
Acute toxicities			
Dermatitis	14 (93%)	1 (7%)	0
Mucotitis	8 (53%)	7 (47%)	0
Total	7 (47%)	8 (53%)	0
Late toxicities			
Edema	14 (93%)	1 (7%)	0
Intestinal obstruction	13 (87%)	2 (13%)	0
Pancreatitis	14 (93%)	1 (7%)	0
Ulcer	14 (93%)	1 (7%)	0
Total	11 (73%)	4 (27%)	0