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特集 乳がんにおける多様性と個別化

センチネルリンパ節転移陽性乳がんにおける腋窩治療*

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Key Words：sentinel node, isolated tumor cells, micrometastases, macrometastases, axillary lymph node dissection

はじめに

センチネルリンパ節生検は，臨床的にリンパ節転移を認めないT1-2N0乳がんにおける標準的なリンパ節転移診断法である[1]．この方法によって見逃される腋窩リンパ節転移の確率は，対象症例のリンパ節転移率を30%，センチネルリンパ節生検に伴う偽陰性率を10%（敏感度を90%）と仮定した場合，3%（=30%×0.1）である．単施設でのセンチネルリンパ節生検後の腋窩リンパ節再発の報告を集計した結果，再発率は年率で0.3%，10年で3%と推定された[2]．乳がんの治療戦略は手術・薬物・放射線を適切に組み合わせた集学的治療である．よって，早期乳がんにおけるセンチネルリンパ節生検に基づく腋窩治療の個別化は，偽陰性例によるリンパ節再発が存在するものの，不必要なリンパ節郭清を省く観点から妥当である[3]．

リンパ節転移の分類とその同定法

Union for International Cancer Control（UICC）第6版からリンパ節転移はその最大径により3つに分類された．いわゆる微小転移は，0.2mm以下のisolated tumor cells（ITC）と0.2mmより大きく2mm以下のmicrometastases（MIC）に分かれ，2mmを超えた転移巣はmacrometastases（MAC）と定義された[4]．センチネルリンパ節を詳細に検討することでITCやMICが高率に同定されるようになったが，その定義に基づく転移巣の計測法はいまだあいまいである（図1）．このような微小ながん細胞集塊を診断するために免疫組織染色はHE染色を補う上で有用であるが[5]，術中の迅速病理診断によって短時間に詳細な転移診断をすることは困難である．One-step nucleic acid amplification（OSNA）法は，サイトケラチン19のmRNAの増幅測定によってリンパ節を転移診断する方法である[6]．その結果，MACとMIC以下の転移巣とを98%の診断精度をもって区分して診断することができた．偽陽性例はなく短時間にリンパ節のMACを診断できることから，OSNA法は病理医による術中迅速病理診断と同等以上のパーフォーマンスが期待される．ただし，カットオフ値の設定からMICとITCの検出率は必ずしも高くないこと，数%存在するサイトケラチン19 mRNAが低発現の乳がんでは偽陰性になることなど課題もある．

センチネルリンパ節微小転移乳がんにおける腋窩治療

センチネルリンパ節生検に関する第III相試験によってリンパ節微小転移の予後への影響が検証された．National Surgical Adjuvant Breast and

* Axilla treatment for sentinel node-positive breast cancer patients.

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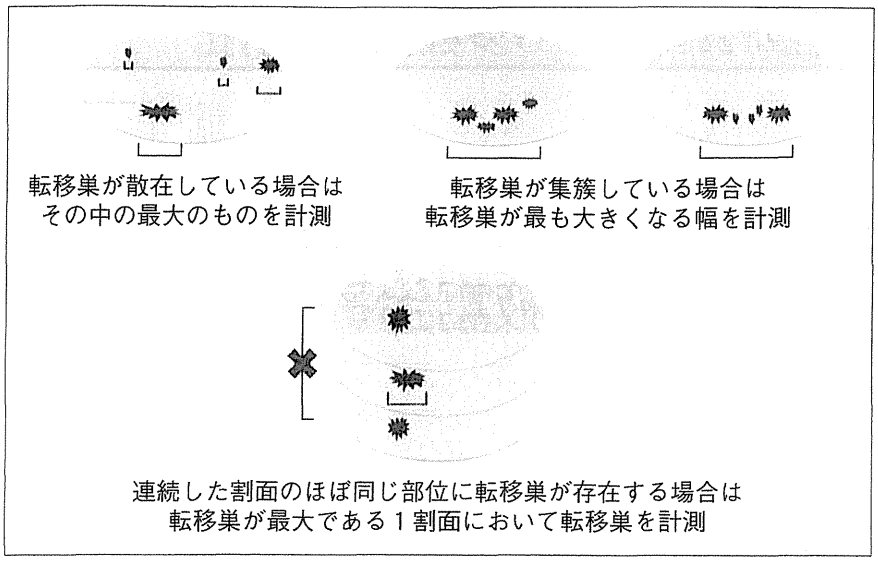

図1　リンパ節転移の計測法
切片作成は短軸でも長軸でも可．1割面に200個未満の細胞からなる腫瘍細胞塊が1つみられる場合はITCと定義．　(Sentinel Node Navigation Surgery研究会案)

Bowel Project Protocol(NSABP) B32試験では，5,611例のT1-2N0乳がんを対象にセンチネルリンパ節生検群とリンパ節郭清群との全生存期間が比較された．3,989例が2 mm間隔でのセンチネルリンパ節のHE染色による病理診断において転移陰性であった．このうち，リンパ節郭清群1,978例とセンチネルリンパ節生検群2,011例との8年全生存率はそれぞれ91.8%と90.3%で差はなかった(P=0.54)[7]．さらに，センチネルリンパ節転移陰性症例3,884例についてリンパ節のブロック検体が回収され，再度0.5mmと1 mmの間隔で深切りを加えてHE染色と免疫組織染色によって発見された潜伏転移の意義が検討された[8]．その結果，ITCが430例にMICが172例にMACが14例に認められた．潜伏転移616例と非潜伏転移3,268例の5年全生存率はそれぞれ94.6%と95.8%であった(P=0.03)．潜伏転移は統計学的に有意な予後不良因子だが，わずか1.2%の差であり補助内分泌療法による予後の改善も認められた．また，リンパ節郭清を省略した症例におけるリンパ節初再発はそれぞれ1.7%と0.5%であった．以上から，センチネルリンパ節を2 mm間隔でHE染色による病理診断を行い転移陰性であれば，潜在的に10%以上存在するITCやMICを見逃しても予後への影響は少なく腋窩のリンパ節郭清は不要である．

センチネルリンパ節マクロ転移乳がんにおける腋窩治療

センチネルリンパ節に転移を認めても，非センチネルリンパ節に転移がなければリンパ節郭清は理論上不要である．センチネルリンパ節にITCまたはMICを認めた症例における非センチネルリンパ節の転移陽性率は，それぞれ0%から26%と6%から57%と報告された[9][10]．一方，術前化学療法によって3割の症例で腋窩のリンパ節転移が病理学的に完全壊死することも報告された[11]．これは，センチネルリンパ節転移陽性乳がんでも薬物療法によって非センチネルリンパ節の転移を含めてがん細胞が消失しリンパ節郭清が不要となる可能性を示している．

American College of Surgeons Oncology Group (ACOSOG) Z0011試験では，T1-2かつセンチネルリンパ節2個以下の転移症例をリンパ節郭清群と非郭清群に無作為に割り付けて2群の予後を比較した．当初予定された1,900例の登録は達成されず856例で試験は打ち切られたが，観察期間6年において非郭清群420例のリンパ節再発はわずか4例(1%)であった[12]．5年全生存率も郭清群と非郭清群で92.5%と91.8%とほぼ同等であった．しかし，この試験には注意すべき点がある．まず，非郭清群の4割はMIC症例であり約8割

図2　術前化学療法後のセンチネルリンパ節生検の妥当性を検証する第II相臨床試験

は1個転移以下症例であったことから，非センチネルリンパ節への転移率は高くないと予想される．次に，本試験は乳房照射を行う乳房温存手術が適格条件であり，線量が不十分としても腋窩が照射野の一部に含まれることによるリンパ節再発の抑止効果が想定された．一方，リンパ節の転移数あるいは転移巣の腫瘍径について登録症例の1割が不明例であった．また，NSABP B32のセンチネルリンパ節転移陰性非郭清群とACOSOG Z0011の転移陽性非郭清群の5年全生存率はそれぞれ95.0%と92.5%であったことから，本試験に登録された症例は比較的予後良好な乳がんが多かったと考えられる[13]．以上より，センチネルリンパ節1個転移の乳房温存症例では，補助薬物療法と乳房照射を行うことでリンパ節郭清は省略可能である．しかし，非センチネルリンパ節の転移遺残は否定できない．画像診断でリンパ節転移を疑う症例，高度のリンパ管侵襲を伴う症例，micropapillary carcinoma症例など，センチネルリンパ節を超えて非センチネルリンパ節までの転移が予測される乳がんではレベルI以上のリンパ節郭清が標準的な腋窩治療である．

臨床的リンパ節転移陽性乳がんの術前化学療法後の腋窩治療

術前化学療法後のセンチネルリンパ節生検の同定率，正診率，偽陰性率に関する成績は，対象となる症例がN0であるかN1以上であるかあらかじめ区別して考える必要がある．もともとセンチネルリンパ節転移陰性症例なのか，化学療法によるリンパ節転移陰性化症例なのか，術前化学療法という括りでセンチネルリンパ節生検の精度が検討されてきたためその成績には幅がある[14]．ACOSOG Z1071はT1-4N1-2乳がんを対象として術前化学療法を行ったあとに，センチネルリンパ節生検を伴うリンパ節郭清を施行してセンチネルリンパ節生検の妥当性を検証する第II相試験である(NCT00881361)(図2)．症例集積はすでに終了しているが，今年の米国臨床腫瘍学会では超音波検査による腋窩リンパ節の転移診断精度が報告されていた(抄録番号1107)．

おわりに

乳がんにおけるリンパ節郭清の省略は，センチネルリンパ節転移陰性症例に加えて転移陽性症例でも適応されつつある．ただし，その前提として腫瘍の悪性度に応じた薬物療法や放射線療法が必須である．がん細胞はリンパ節，骨髄など潜在的に存在するものの臨床的に顕性化しないtumor dormancyの状態が存在する．乳がんでは5年以上経過したあとの臨床的再発が稀ではない．ACOSOG Z0011の結果も非センチネルリンパ節におけるtumor dormancyが示唆される．腋窩リンパ節転移再発だけでは生命予後に影響しないとする見方もあるが，リンパ節郭清が省略される時代に入って，遺残したリンパ節転移巣を起点にがん細胞が全身に播種しないのか不明である．腋窩への外科的侵襲は最小限に止めるべきであるが，臨床病理学的所見から非センチネルリンパ節転移の可能性を症例ごとに検討した上で腋窩治療の個別化を進めるべきである．

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総　説

乳癌治療の現状と展望

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要　旨

乳房温存療法，センチネルリンパ節生検，ラジオ波焼灼治療，遺伝子発現に基づく薬物治療，そして分子標的治療の現状と展望について概説する。外科治療は乳房部分切除とセンチネルリンパ節生検によって，乳房を喪失し，術後リンパ浮腫などの後遺症に悩まされる患者を半減させた。また，マンモグラフィ検診や超音波検診によって，早期乳癌の発見率が高まっている。そこで，ラジオ波焼灼治療は乳管内進展が限局した早期乳癌において，乳房温存療法と同等の治療効果が期待されるため，現在臨床試験を行っている。一方，薬物治療はER，HER2，Ki67の分子マーカーを指標とした特性に基づいて治療方針が決められている。よりきめの細かい薬物治療の個別化として遺伝子発現に基づく薬物治療と分子標的治療の開発が進められている。

緒　言

近代的な乳癌治療は19世紀後半に始まり，1970年代までは手術がその根幹を成していた。しかし，早期から骨髄中[1]あるいは末梢血中[2]に癌細胞が存在する乳癌の疾患特異性から自ずと外科治療には限界があった。1980年代に入り，早期乳癌に対する外科治療として，乳房全切除に替わって乳房部分切除と温存乳房照射を併用した乳房温存療法が確立した。1990年代には，腋窩リンパ節郭清（以下，郭清）に替わって，臨床的リンパ節転移陰性であるN0乳癌に対するセンチネルリンパ節生検が提唱され[3]，センチネルリンパ節転移陰性であれば郭清が省略されるようになった。一方，薬物治療では1990年代からpaclitaxelやdocetaxelなどさまざまな化学療法剤が導入された。2000年代にはHER2に対する分子標的治療が開発された[4]。現在は，ホルモン感受性の指標であるERの陽性率や細胞周期の指標であるKi67の発現，そしてHER2の発現など効果予測因子に基づいた薬物治療が一般的である。多岐にわたって日進月歩の乳癌治療であるが，乳房温存療法，センチネルリンパ節生検，ラジオ波焼灼治療，遺伝子発現に基づく薬物治療，そして分子標的治療の現状と展望を述べる。

乳房温存療法

National Surgical Adjuvant Breast and Bowel Project（NSABP）B06による4 cm以下のT1-2乳癌に対する乳房部分切除と乳房全切除を比較した第III相臨床試験では，10年乳房内再発率は約10％であり両群の生存率は同等と報告された[5]。3 cm以下の日本人女性乳癌1,901例を対象とした乳房温存療法に関する多施設共同研究では，10年生存率と健存率は84％と78％で，同側乳房内の10年累積再発率は乳房照射群で8.5％，乳房非照射群で17.2％であった[6]。多変量解析による同側乳房内再発の独立した危険因子は，若年，切除断端陽性と乳房非照射であった。乳癌術後の乳房照射を含む放射線治療に関する臨床試験のメタアナリシスでは，5年局所再発率を10％未満と10％以上との2群に分けた場合，後者の方が生命予後は不良であった[7]。MRIによる正確な乳管内進展巣の予測に基づいた乳房の切除が可能となった現在だが，乳房温存療法の基本は適切な範囲の乳房切除と温存乳房の照射であることに変わりはない。

センチネルリンパ節生検

センチネルリンパ節とは，腫瘍からのリンパ流を最初に

Key words:　breast cancer, sentinel node biopsy, molecular targeted therapy, radiofrequency ablation therapy

受けるリンパ節であり，癌の転移を見張るリンパ節である。このリンパ節を色素やアイソトープなどのトレーサーによって同定し生検を行い，病理学的あるいは分子生物学的に転移の有無を診断する方法がセンチネルリンパ節生検である。約8,000例のセンチネルリンパ節生検に関するメタアナリシスの結果，センチネルリンパ節の同定率は96％で偽陰性率は7％であった[8]。腫瘍免疫学からも機能生理学からも，あらゆる固形癌の所属リンパ節の中にセンチネルリンパ節は存在するはずである。しかし，その局在を診断する難易度，所属リンパ節再発時の診断と治療の難易度，そして個々の癌種における外科治療，薬物治療，そして放射線治療の奏効の有無などを考慮した場合，必ずしもセンチネルリンパ節生検の実行可能性と実地臨床への導入は容易でない。

N0乳癌に対するセンチネルリンパ節生検の予後への影響を検証すべく，1990年代末から欧米では大規模な臨床試験が行われた。日本では2004年からSentinel Node Navigation Surgery（SNNS）研究会が早期乳癌におけるセンチネルリンパ節生検に関する前向き研究を行った。筆者は登録された約1,400例の解析と5年間の予後調査から，センチネルリンパ節生検に関する高い同定率（98％）とセンチネルリンパ節転移陰性乳癌での良好な予後についてそれぞれ報告した[9,10]。

現在，郭清のさらなる個別化を進めるべく，非センチネルリンパ節の転移予測や，術前化学療法後のセンチネルリンパ節生検の妥当性や，僅かにセンチネルリンパ節に転移巣を有する乳癌における非郭清の妥当性が検証されている。

固形癌においてリンパ節転移陽性であれば，所属リンパ節の郭清を行うことは自明の理と思われる。しかし，センチネルリンパ節のみに転移があるのであれば非センチネルリンパ節を郭清する必要はないかも知れない。杏林大学医学部付属乳腺外科では，欧州の12施設と共同でセンチネルリンパ節転移陽性症例における非センチネルリンパ節転移の予測式とその妥当性について検討した[11]。予測式の因子は，各施設での非センチネルリンパ節転移率，脈管侵襲，多中心性，HER2発現，センチネルリンパ節転移陽性数と陰性数，腫瘍径，リンパ節転移径の分類と節外浸潤であった（http://www.hus.fi/breastsurgery/predictivemodel）。その結果，internal validation 500例とexternal validation 1068例におけるAUCはそれぞれ0.714と0.719であった。予測値のカットオフをどこに置くのか課題はあるものの，予測値に画像診断を加えることでセンチネルリンパ節転移陽性であっても郭清省略を考慮することが可能である。

American College of Surgeons Oncology Group (ACOSOG) Z1071は，リンパ節転移陽性（N+）乳癌を対象に術前化学療法後にセンチネルリンパ節生検と郭清を行う第II相試験である（図1）。Primary endpointは，センチネルリンパ節転移と非センチネルリンパ節転移の有無から算出される偽陰性率である。本来であれば郭清が基本となるN＋乳癌であるが，術前化学療法によって3割の症例でリンパ節転移が陰性化することが報告された[12]。化学療法によってリンパ節転移が陰性化するならば，郭清を省略しても予後に影響を与えないはずである。本研究の結果は近々に報告される予定である。

1970年代にN0乳癌を対象とした郭清を伴う根治的乳房全切除，乳房全切除＋腋窩照射，そして郭清を伴わない単純乳房全切除の3群を比較する第III相試験が行われた(NSABP B04)[13]。その結果，単純乳房全切除群のリンパ節再発は18％であった。一方，郭清を伴う根治的乳房全切除群の病理学的リンパ節転移症例は30％であったことから，単純乳房全切除群にはリンパ節転移が存在しても再発として顕性化しない症例が想定された。理由として，単純乳房全切除時にリンパ節も合併切除された可能性があった。しかし，薬物治療が行われていない時代でもあり，宿主と腫瘍の免疫応答によるtumor dormancyもリンパ節再発が顕性化しない一因と考えられる。そこで，センチネルリンパ節生検の時代に入って，0.2 mmから2 mmのミクロ転移を認めた症例と2個以下のマクロ転移を認めた症例を対象に，センチネルリンパ節生検後の郭清と非郭清の全生存率を比較する第III相試験が行われた（ACOSOG Z0011）。郭清群の優越性を証明するために目標症例は1,900例であった。1999年から891例が登録され，予想に反してイベント数が少なく届かず2004年に中止された[14]。しかし，観察期間の中央値が6年で，5年全生存率は郭清群445

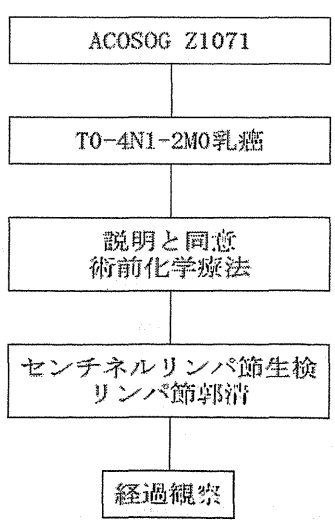

図1　ACOSOG Z1071スキーム
(Primary endpointはセンチネルリンパ生検偽陰性率。目標660例登録終了)

例が91.8％で非郭清群446例が92.5％であり，局所または所属リンパ節の再発は僅かに16例と12例であった。その結果，ACOSOG Z0011と同じ基準に該当する乳房温存療法症例であれば，センチネルリンパ節にミクロ転移や2個以下のマクロ転移を認めても郭清を省略する方向に向かっている。但し，本試験ではT1症例，ミクロ転移症例，1個転移症例など非センチネルリンパ節転移の頻度が少ない対象が多く含まれていたことから，2個以下のマクロ転移症例の全てを非郭清とするには十分な根拠に乏しい。SNNS研究会では，センチネルリンパ節にミクロ転移あるいは3個以下のマクロ転移を認めた症例を郭清の有無に寄らず集積して，非郭清時のリンパ節再発に関するコホート研究を計画中である。

ラジオ波焼灼治療

ラジオ波焼灼治療（radiofrequency ablation，以下RFA）とは，腫瘍を焼灼して細胞死させる治療法である。肝細胞癌はウィルス性悪性疾患であり腫瘍切除後も高頻度に肝臓内に再発することから，RFAは侵襲の少ない治療法の一つとして保険診療で行われている。また，転移性骨腫瘍ではRFAが疼痛緩和に有効であると報告された[15]。このような対症療法としてのRFAに対して，0-I期乳がんにおけるRFAの意義は乳房部分切除術と同等の治療の質を保ちながら，乳房の変形が少なく患者に優しい医療を実現することが目標である。RFA後に乳房切除を行ったfeasibility studyを表1に示す[16]。どの報告も症例数が少なくエビデンスレベルが高いとは言えないが，T1乳がんを対象とした試験では177例中152例（86％）で病理学的な完全焼灼（腫瘍壊死）を得た。主な有害事象である皮膚熱傷は全症例中11例（4％）であった。以上から，超音波ガイド下による腫瘍穿刺については習熟（learning curve）を要するが，広範な乳管内進展を伴わない乳がんに対してRFAの安全性と実行可能性が示唆された。

2005年に発足した乳癌低侵襲治療研究会では，早期乳がんを対象としたRFA，凍結療法，MRIガイド下収束超音波術など治療法の開発に取り組んでいる。臨床試験ある

表1　早期乳がんに対する乳房切除を伴うRFAのfeasibility study（文献15より改変）

報告者（年）	腫瘍径	電極針	症例数	完全焼灼率（％）	有害事象(症例数)
Jeffrey (1999)	T2-T3	LeVeen	5	4 (80)	なし
Izzo (2001)	T1-T2	LeVeen	26	25 (96)	皮膚熱傷 (1)
Burak (2002)	T1	LeVeen	10	9 (90)	なし
Singletary (2003)	T1	RITA	29	25 (86)	皮膚熱傷 (1)
Hayashi (2003)	T1	RITA	22	14 (64)	皮膚熱傷 (1)
					創感染 (1)
Noguchi (2006)	T1	RITA	10	10 (100)	なし
Khatri (2006)	T1	Cool-Tip	15	14 (93)	皮膚引きつれ (2)
Medina-Franco (2008)	T1-2	Elektrotom	25	19 (76)	皮膚熱傷 (3)
					創感染 (1)
Imoto (2009)	T1	LeVeen	30	26 (87)	皮膚熱傷 (2)
					胸筋熱傷 (8)
Kinoshita (2011)	T1-2	Cool-Tip	49	30 (61)	皮膚熱傷 (2)
					胸筋熱傷 (3)
Hung (2011)	T1	LeVeen/Cool-Tip	20	18 (90)	なし
Ohtani (2011)	T1	Cool-tip	41	36 (88)	皮膚熱傷 (1)
全体	T1-3	Various	282	234 (83)	皮膚熱傷 (11)
					その他 (18)
T1対象			177	152 (86)	

いは実地臨床として施行されたRFA 521例の後向き解析の結果，腫瘍径が2 cm以下であればRFA後の5年乳房内無再発率は95.6％であった[17]。以上から，乳管内進展が限局した0-I期乳がんであれば，乳房部分切除術の替わりにRFAを施行し乳房照射を併用することで，現行の乳房温存療法と同等の治療効果が期待される。当研究会では，乳管内進展が限局した0-I期乳がんを対象としたRFAに関する第II相試験を2012年11月に開始した。Primary endpointはRFA後1ヶ月時点での組織生検に基づく病理学的な完全腫瘍焼灼率であり，secondary endpointはRFAの安全性，整容性と10年無再発生存率と10年全生存率である（図2）。

遺伝子発現に基づく薬物治療

乳癌の古典的な予後因子は核異型度または組織異型度，リンパ節転移，脈管侵襲などである。2000年代に入って乳癌関連の遺伝子発現に基づいた再発リスク分類が提唱された。その代表として，OncotypeDxでは21遺伝子を[18]，MammaPrintでは70遺伝子の発現に基づいて再発リスクが分類された[19]。乳癌の遺伝子発現の結果から，ER陽性かつ低リスク乳癌では内分泌療法に加えて化学療法を上乗せする効果が小さいことが報告された[20]。これを受けて，OncotypeDxは米国で，MammaPrintは欧州で，それぞれ再発リスク分類に基づいた薬物治療の個別化，特に化学療法の上乗せ効果を検証する第III相試験が進行中である。なお，検査価格は数十万円であり本邦では保険診療外である。但し，リスク分類の妥当性が前向きに証明されれば不必要な化学療法を行う医療費の削減が期待される。今後，遺伝子検査の簡便化と低価格化が実現すれば，その費用対効果から見て保険診療に組み込まれる可能性は十分にある。

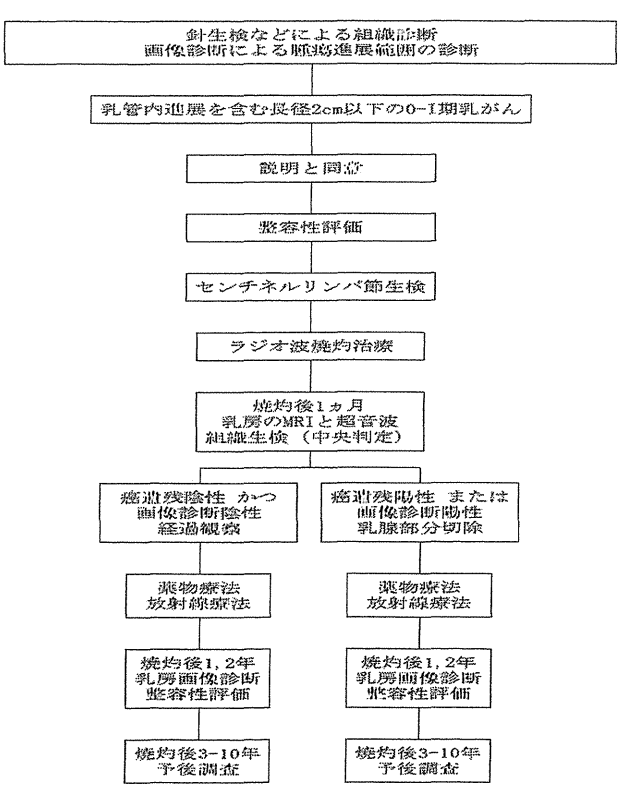

図2　ラジオ波焼灼治療の第II相臨床試験

分子標的治療

最近の網羅的な遺伝子解析によって，増殖速度が比較的遅いと考えられるER陽性で高分化型のluminal A-type乳癌であっても，PI3K・AKT・mTORのシグナル伝達系の異常やCDK4/6・RB・E2FなどG1期で細胞周期を抑制する遺伝子群に高率に異常を認めることが報告された[21]。そこで，ER陽性の進行再発乳癌においてステロイド骨格アロマターゼ阻害剤単独とmTOR阻害剤であるeverolimusの併用療法を比較した第III相試験が行われた[22]。その結果，従来の2次内分泌療法に比べて有意な無増悪期間の延長が認められた（6.9ヵ月対2.8ヵ月，Hazard ratio 0.43）。本試験では，非ステロイド骨格のアロマターゼ阻害剤治療後の進行再発乳癌症例が対象であったことから，シグナル伝達系の抑制がホルモン感受性を高めたことが示唆された。今後，HER2-type乳癌では抗HER2剤であるtrastuzumab，lapatinibに加えてpertuzumab，T-DM1などが臨床導入される予定である。さらに，ER陰性HER2陰性のbasal-type乳癌では家族性乳癌の責任遺伝子であり2本鎖DNAの修復機能を有するBRCA1あるいはBRCA2の機能不全が高率に認められるため，抗がん剤に加えてPARP阻害剤を併用した合成致死（synthetic lethality）による治療戦略が試みられている。乳癌の薬物治療は，予後不良因子に基づく治療選択から分子レベルでの効果予測因子に基づく分子標的治療の時代に入っている。

結　語

多岐にわたる乳癌治療の中でいくつかの課題についてその現状と展望を概説した。今後，注目すべき課題として宿主と腫瘍と治療との関係が挙げられる。宿主と腫瘍の免疫応答とそのバランスの変化は，乳癌でしばしば見られる5年ないし10年後の臨床的な再発に関与している。Tumor dormancyとは宿主と腫瘍との微小環境におけるせめぎ合いである。一方，日本人女性の乳癌罹患率は40歳代にピークがあり，欧米女性の60歳代のピークと比べて早い時期に来ることは，発癌過程における女性ホルモンの産生と代謝の影響が人種間で異なることを示唆している。癌の個性に応じた集学的治療に加えて，患者個々の背景を考慮したオーダメードの乳癌治療もこれからの重要な課題である。

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ORIGINAL ARTICLE

Surgical management of small bowel metastases from primary carcinoma of the lung

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Abstract
Purpose To investigate the treatment and outcomes in a series of seven cases of small bowel metastases from lung cancer.
Methods A total of 4114 patients with lung cancer were referred to this institution from 1995 to 2005. Seven (0.17%) developed symptomatic small bowel metastasis and were treated surgically. The clinical, radiological, and pathological records were reviewed.
Results Small bowel metastases were diagnosed from 0 to 31 months (mean 11.5 months) after the diagnosis of lung cancer. The clinical symptoms at presentation were acute peritonitis in two patients and abdominal pain in five. Small bowel metastasis was suspected on abdominal X-ray in three cases, computed tomography in two, small bowel radiography in one, and endogastroduodenoscopy in one. All patients underwent surgery and there were no perioperative deaths. Intestinal resection was performed in five cases and a bypass in two. A small bowel metastasis was found in the ileum in four patients. The mean survival period was 7.7 months after surgery. One patient lived for 22 months after bowel resection. Oral intake was possible 1 month after surgery in six cases.
Conclusion Surgical management should be considered as palliative treatment in patients with a bowel obstruction or peritonitis caused by primary lung cancer.

Keywords Lung cancer · Small bowel metastasis · Surgical management · Small bowel tumor · Oral intake

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Introduction

Approximately half of all lung cancer cases are inoperable at the time of diagnosis, due to metastasis to various organs including the brain, liver, bones, and adrenal glands [1–3]. Although postmortem examinations demonstrate that gastrointestinal metastasis is not uncommon in patients with lung cancer, it is rarely found in clinical situations because only a few patients are symptomatic [4–7]. The common symptoms of gastrointestinal metastases are abdominal pain, gastrointestinal bleeding, obstruction, intussusceptions, and perforation [6, 8, 9], of which perforation is the most serious complication, most often associated with small bowel metastasis that necessitates surgical resection to prevent a life-threatening event. The most common and dangerous presentation is small bowel perforation, which often leads to death.

Improved awareness of gastrointestinal tract metastasis among physicians is important, since the incidence of lung cancer is increasing and patients with lung cancer now live longer due to improvement in treatment. This study reviewed cases of gastrointestinal metastasis of lung cancer

over an 11-year period at a single institution in Japan. The aim of the study was to evaluate the frequency of metastasis to the gastrointestinal tract from primary lung cancer, and to report the clinical characteristics and outcomes of these patients after surgery. The postoperative quality of life (QOL) for patients who underwent palliative surgery was also evaluated in terms of oral intake after the procedure.

Patients and methods

This study examined the records of all patients with pathological evidence of gastrointestinal metastasis with a diagnosis of primary lung cancer at the Pathology Section, National Cancer Center Hospital East, over 11 years (from 1995 to 2005). All available reports and some slides were carefully studied and re-examined. Information obtained included the age, sex, pathology, location of primary lung cancer, clinical presentations, diagnostic procedures, other metastatic sites at the time of gastrointestinal metastasis, interval between the diagnosis of the lung tumor and discovery of the metastasis, survival, and the term of oral intake after surgery. Histological types were classified according to World Health Organization guidelines as small cell carcinoma, adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, large cell carcinoma, and others, including unclassified types. Gastrointestinal metastases included cases with direct mucous metastasis to the gastrointestinal tract, but excluded those with direct invasion from the abdominal lymph nodes and abdominal dissemination. The characteristics of the patients with and without gastrointestinal metastasis were compared.

Results

A total of 4114 patients with lung cancer were referred to this institution from 1995 to 2005. Seven (0.17%) developed symptomatic small bowel metastasis. The clinical and pathological findings in the seven patients are shown in Table 1. The median age of these patients was 59.6 years at the time of diagnosis of small bowel metastasis, and all of the patients were male. The patients were pathologically diagnosed with small bowel metastasis from lung carcinoma. Six patients had adenocarcinoma and one had squamous cell carcinoma. The mean period between the diagnosis of the lung tumor and discovery of the bowel metastasis was 349 days. The clinical symptoms included abdominal pain in five cases and peritonitis in two cases. A free air sign was found in three patients on abdominal X-ray and in two patients by computed tomography (CT).

The surgical findings and outcome for the seven patients are shown in Table 2. Resection of the primary tumor was

Table 1 Clinical and pathological findings in seven patients with small bowel metastases

	Patient number						
	1	2	3	4	5	6	7
Age (years)/ sex	55/M	58/M	40/M	56/M	78/M	62/M	68/M
Pathological diagnosis	Adenocarcinoma (P/D)	Adenocarcinoma (P/D)	Adenocarcinoma (P/D)	Adenocarcinoma (P/D)	Squamous cell carcinoma (P/D)	Adenocarcinoma (W/D)	Adenocarcinoma (P/D)
Primary site	T1N0	T4N1	T2N3	T2N3	T4N2	T1N0	T4N1
Delay between diagnosis of lung tumor and discovery of bowel metastasis (days)	0	522	201	275	69	443	933
Clinical presentation	Abdominal pain	Peritonitis	Peritonitis	Abdominal pain	Abdominal pain	Abdominal pain	Abdominal pain
Diagnostic procedure	Abdominal X-ray	Abdominal X-ray	Abdominal X-ray	EGD	CT scan	Upper GI	CT scan
Other metastatic sites	Liver, brain	Colon	Brain	Liver, abdominal LN	Lung, liver, bone, adrenal, abdominal LN	None	Brain, bone

P/D poorly differentiated, *W/D* well differentiated, *Upper GI* upper GI series, *EGD* esophagogastroduodenoscopy, *CT* computed tomography, *LN* lymph nodes

Table 2 Surgical findings and outcome in seven patients with small bowel metastases

	Patient number						
	1	2	3	4	5	6	7
Primary site of operation	None	None	None	None	None	RUL	None
Intraoperative findings	Perforation	Perforation	Perforation	Stenosis	Perforation	Stenosis	Stenosis
Bowel metastasis	Ileum	Jejunum	Ileum	Duodenum	Ileum	Jejunum	Ileum
Bowel metastasis operation	Partial resection, drainage	Partial resection, drainage	Partial resection, drainage	Bypass	Partial resection, drainage	Partial resection, drainage	Bypass
Operation time (min)	107	102	130	75	105	92	101
Postoperative oral intake (days)	31	56	286	0	34	679	217
Survival (days)	53	108	347	25	67	742	302

RUL right upper lobectomy

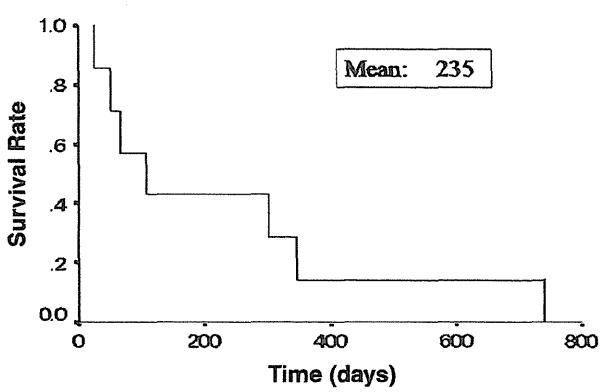

Fig. 1 Postoperative survival of patients with small bowel metastases from primary carcinoma of the lung. The mean survival period was 234 days and the median was 108 days

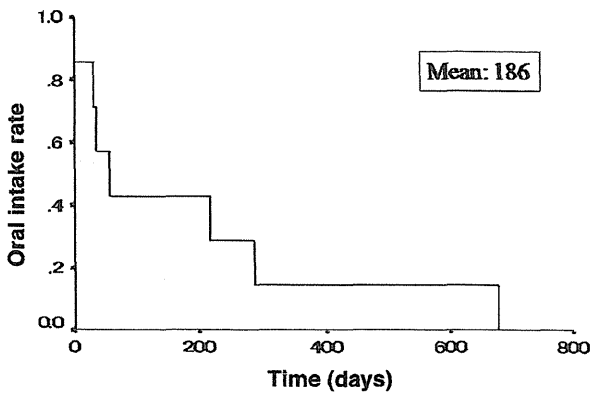

Fig. 2 Periods for which oral intake was possible are shown as an indicator of postoperative quality of life. Oral intake was possible for an average of 186 days after small bowel surgery

performed in one patient only. The other six patients were followed while receiving treatment for lung carcinoma. Metastasis was observed in the ileum in four patients (57.1%) and in the jejunum in two patients (28.6%). Partial resection of the small bowel including the metastatic lesion was performed in five patients and bypass surgery was performed in two patients, in which a resection was difficult. The mean operation time of 1 h 41 min for these procedures was relatively short. No serious postoperative complications were associated with the surgery in the cases included in this study. Patient 4 died of respiratory failure associated with acute exacerbation of the primary carcinoma of the lung 25 days after the operation. The mean overall survival period was 234 days, the mean survival period was 235 days, and three patients survived for 300 days or more after the operation (Fig. 1). Oral intake was possible for a mean period of 186 days after the small bowel surgery (Fig. 2).

Discussion

Many patients with small bowel metastasis from primary carcinoma of the lung undergo palliative surgery. The postoperative prognosis of small bowel metastasis is often poor, but some studies have reported good survival after bowel resection [3]. Yang et al. [1] reported an average period of 130.3 days from diagnosis of gastrointestinal metastasis to death, indicating a poor prognosis. This survival time is similar to the findings in the current series of seven patients. Maintenance of a good postoperative QOL through oral intake is also important, and has not been evaluated previously in patients with small bowel metastasis. The mean period of oral intake was 186 days after small bowel resection, which suggests that the surgical treatment was effective in maintaining the QOL of the patients.

The clinical prevalence of gastrointestinal metastasis in the current study was 0.17% (7/4114), which is much lower than in previous reports [1, 5, 7]. Gastrointestinal

metastases from lung cancer in the stomach, small intestine, and large intestine occur in 7.3–12.2% of autopsy cases [5, 7]. However, the prevalence is likely to be higher in an autopsy series because the majority of patients with gastrointestinal metastases are asymptomatic. It is probable that more patients will present with associated symptoms in the future, due to advances in the treatment of lung cancer increasing survival. Improved diagnostic methods are also better able to detect occult metastases. [^{18}F]Fluorodeoxyglucose positron emission tomography (FDG-PET)/CT can be used for the detection of gastrointestinal metastasis of lung cancer [10, 11], and for the staging of lung cancer and identification of incidental secondary malignancies or occult metastases of primary cancer. This technique was not used in the current study, but FDG-PET/CT is likely to become important for the detection of small bowel metastases from a primary carcinoma.

The differential diagnosis of malignant lymphoma, small bowel cancer, leiomyosarcoma, and carcinoid tumors requires histological diagnosis of biopsy specimens. Therefore, these lesions are often considered collectively as small bowel carcinoma in laboratory tests and in clinical treatment. However, recent progress with small bowel endoscopy has facilitated the definitive diagnosis of small bowel diseases [12, 13]. Capsule endoscopy is a noninvasive and desirable test method, but cannot be used for biopsy and in cases requiring hemostasis. Therefore, double-balloon endoscopy is recommended if systemic symptoms permit. In some cases, double-balloon endoscopy may allow small bowel metastases from primary carcinoma of the lung to be diagnosed by biopsy alone without the use of laparotomy.

The ileum was the most common site of metastasis from lung cancer in the current series, which is consistent with previous studies [1, 8]. Metastasis to the jejunum occurs at a slightly lower prevalence in comparison to the ileum [6, 8], and metastasis to the duodenum is relatively rare [14, 15]. Small bowel involvement often leads to perforation, obstruction, or bleeding [8, 15–18]. Bowel perforation is the most common presentation for both adenocarcinoma and squamous cell carcinoma [8]. Yoshimoto et al. [2] showed that gastrointestinal metastasis and life-threatening events occur more often in patients with large cell carcinomas. Gastrointestinal bleeding develops more commonly with large cell carcinoma [19]. Poorly differentiated adenocarcinoma of the lung was the most frequent form of primary cancer in the present series, and all the patients required surgery to relieve perforation or obstruction. Emergency surgery was needed because of perforation in four patients. Early diagnosis using a technique such as FDG-PET/CT may reduce the need for emergency operations.

Deteriorated systemic symptoms are observed is some cases, due to bleeding from the carcinoma during palliative surgery. Partial resection of the small bowel including the metastatic lesion is preferable is such cases. Partial resection of the small bowel was performed in five of the current patients. However, bypass surgery may be more effective in avoiding excessive surgical invasion in patients with conditions such as profound carcinoma infiltration. This approach may be preferable in terms of the postoperative QOL, since the oral-intake period may be extended.

The prognosis of small bowel metastasis from the lung is thought to be very poor, but there were no cases of perioperative death, and oral intake was possible after surgery for longer than 1 month in six cases. These results show that surgical treatment can lead to a good outcome in patients with small bowel metastasis. Partial resection of the small bowel is required in cases with perforation, but not in those with stenosis, which can be treated with palliative surgery. In conclusion, surgical management should be considered as the best palliative treatment in patients with bowel obstruction or peritonitis caused by primary lung cancer.

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Conflict of interest Yuji Nishizawa and the other co-authors have no conflict of interest.

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ORIGINAL ARTICLE

Predictive Factors for Anastomotic Leakage after Simultaneous Resection of Synchronous Colorectal Liver Metastasis

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Abstract
Background The optimal surgical strategy for resectable, synchronous, colorectal liver metastases remains unclear. The objective of this study was to determine which patients could benefit from staged resections instead of simultaneous resection by identifying predictive factors for postoperative morbidity and anastomotic leakage after simultaneous resection of synchronous, colorectal liver metastases and the primary colorectal tumor.
Methods This study involved 86 patients with synchronous colorectal liver metastases who underwent simultaneous resection of the primary colorectal tumor and the hepatic tumor. Postoperative mortality, morbidity, and other surgical outcomes, including survival and hospitalization, were assessed. Predictive factors for postoperative morbidity and for anastomotic leakage were evaluated.
Results Postoperative morbidity and anastomotic leakage were found in 55 (64%) and 18 (21%) patients. Predictive factors for postoperative morbidity and for anastomotic leakage were intraoperative blood loss and operation time >8 h, respectively. The overall 5-year survival rate was 45%.
Conclusions The frequency of morbidity and that of anastomotic leakage seemed to be high after simultaneous resection for synchronous colorectal liver metastases, especially when intraoperative blood loss or operation time increased greatly. Staged resections should be considered in cases in which excessive surgical stress from simultaneous resection of synchronous colorectal liver metastases would be expected.

Keywords Colorectal cancer · Hepatic metastasis · Liver metastasis · Morbidity · Anastomotic leakage

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Introduction

For patients with synchronous colorectal liver metastases (SCLM), hepatic resection is considered the best treatment, with reported 5-year survival rates between 23% and 37%.[1–4] Resections of both the primary colorectal lesion and the hepatic metastases are needed for patients with SCLM when they are resectable. However, the optimal surgical strategy for resectable SCLM still remains controversial.

From the perspectives of less operation with less mental stress and simplifying perioperative treatment, simultaneous resection of the primary colorectal and liver tumors is a favorable strategy for patients with SCLM.[5–8] However, several papers reported that the morbidity rate after simultaneous resection of primary and liver tumors was high because of greater surgical stress and a longer

operation time than for single-organ surgery. Staged resection with initial operation for the primary lesion followed by resection of hepatic tumors is regarded as an alternative strategy to avoid excessive surgical stress for patients with SCLM, though the efficacy of this strategy and the patients who could benefit from this strategy are unknown.[4–6,9,10]

Thus, this study was conducted to determine which patients could benefit from staged resections instead of simultaneous resection by identifying predictive factors for postoperative morbidity and anastomotic leakage after simultaneous resection of SCLM.

Patients and Methods

Patient Population

The medical records of all consecutive patients who underwent liver resections for colorectal liver metastases from January 1992 to January 2004 at our institution were analyzed retrospectively, with institutional review board approval. Eighty-six patients had SCLM. During this period, all SCLM patients received simultaneous resection of primary colorectal and hepatic tumors irrespective of the patient's or the tumor's characteristics. Lateral lymph node dissection was routinely performed in patients with advanced lower rectal cancer. All 86 patients underwent contrast enhanced computed tomography (CT) of the chest, abdomen, and pelvis, as well as hepatic MRI, preoperatively.

As a control, the morbidity of 167 patients who underwent hepatectomy for metachronous liver metastasis from colorectal cancer from January 1992 to January 2004 and that of 1,728 patients who underwent only resection for colorectal cancer with colorectal reconstruction during the same period were also reviewed. Of the 1,728 colorectal cancer patients, 1,319 had colon cancer and 409 had rectal cancer.

Postoperative Morbidity

Incidences of the following postoperative complications were analyzed: anastomotic leak, rectovaginal fistula, intraperitoneal or pelvic abscess, wound infection, wound dehiscence, ileus, enteroparesis, postoperative delirium, urinary tract infection, dysuria, empyema thoracis, pleural effusion, atelectasis, cholecystitis, perihepatic or subphrenic abscess, bile leak, liver failure, and others. Anastomotic leakage was defined as follows: peritonitis and a dehiscence in the anastomosis, discharge of pus from the anus, vaginal fistula, or feces from the abdominal drain. Leakage was confirmed by CT scan, contrast enema, re-operation, or digital rectal examination. All complications were graded according to the classification proposed by Clavien et al.[11] Postoperative mortality was defined to include any death during postoperative hospitalization or within 30 days.

Assessment of Predictive Factors for Postoperative Morbidity

Correlations between postoperative morbidity and the following patient, tumor, and surgical factors were analyzed: age, sex, body mass index (BMI), preoperative comorbidity, site of primary tumor, intestinal obstruction by tumor, size of primary tumor, differentiation of tumor, distribution of hepatic tumors, number of hepatic tumors, hepatic tumor size, operative methods, operation time, intraoperative blood loss, and blood transfusion.

Survival

Patients were followed regularly at 3-month intervals with blood testing and CT. Survival and follow-up were calculated from the time of the operation to the date of death or last available follow-up. The survivors' median follow-up time after surgery was 73 months.

Statistical Analysis

Statistical comparisons of baseline data were performed using the chi-square test. Continuous variables were compared with the independent t test. Multivariate analyses to evaluate the independent predictive factors for postoperative complications or anastomotic leakage were done by multiple logistic regression analysis. The survival rate was calculated by the Kaplan–Meier method.[12] A difference was considered significant when p was less than 0.05.

Results

Patients and Operative Details

From 1992 to 2004, 86 patients were treated with simultaneous resection of primary and hepatic tumors for SCLM. There were 37 female and 49 male patients, with a median age of 59 years (range, 40 to 85 years). The site of the primary tumor was colon in 48 and rectum in 38. The primary tumor was staged as T3 in 54 (63%) and T4 in 32 (37%) according to the TNM classification. Metastatic lymph nodes were found in 65 patients (76%). The mean diameter of the primary tumor was 55 mm (range, 26–140 mm).

Liver metastases were solitary in 29 patients and multiple in 57 patients. In 47 patients (55%), the hepatic

tumor showed a unilobar distribution, while a bilobar tumor distribution was observed in 39 (45%). The mean diameter of the hepatic tumor was about 43 mm (range, 5–200 mm). The mean resected liver volume was 380 g (range, 10–1,660 g).

The operation for primary colorectal cancer was right (hemi) colectomy in 17 patients, transverse colectomy in 1, left (hemi) colectomy in 4, sigmoidectomy in 24, high anterior resection in 7, low anterior resection in 20, very low anterior resection in 6, inter-sphincteric resection in 2, Hartmann's operation in 1, and abdomino-perineal resection in 4 (Table 4). A diverting stoma to prevent anastomotic leakage was made in 22 (26%) patients at the surgeon's discretion, and lateral lymph node dissection was performed in 20 (23%). In terms of liver tumor resection, lobectomy was performed in 11 patients, segmentectomy in 22, bisegmentectomy in 1, trisegmentectomy in 2, subsegmentectomy in 3, and partial resection in 47.

Adjuvant therapy was given to only 17 patients (19.8%) because adjuvant chemotherapy for colorectal cancer in stage III or more was performed since January 2003. Neoadjuvant chemoradiation targeting for rectal cancer was given to three patients (3.5%).

Morbidity

No patients died within 30 days of the operation, but 55 (64%) patients developed complications (Table 1). Eighteen patients (21%) experienced leakage, of whom 6 needed urgent re-operation with ileostomy and drainage of an intra-abdominal collection caused by leakage. Postoperative bleeding, wound dehiscence, and ileus were the reasons for the three other re-operation cases. The most frequent complication was wound infection.

The morbidity rate of the 167 patients who underwent hepatectomy for metachronous colorectal liver metastasis during the same period was 19.8%, and that of 1,728 patients who underwent only resection for colorectal cancer was 32.1%. Anastomotic leakage occurred in 123 (7.1%) of the aforementioned 1,728 patients.

Factors Affecting Complications, Especially Anastomotic Leakage

Postoperative complications were significantly correlated with presence of diverting stoma ($p<0.01$), duration of operation greater than 8 h ($p<0.01$), amount of intra-operative blood loss ($p<0.01$), and intraoperative blood transfusion ($p<0.01$). The aforementioned factors were entered into multivariate analysis. Only a greater amount of blood loss had a predictive value for increased occurrence of postoperative complications.

Then, the correlations between anastomotic leakage and clinicopathological factors were examined to identify risk factors for anastomotic leakage after simultaneous resection for SCLM. Patients who underwent abdomino-perineal

Table 1 Postoperative complications after simultaneous resection for SCLM according to Clavien grade

Complications	No. of patients	Gr I	Gr II	Gr IIIa	Gr IIIb	Gr IVa
Colon and rectum						
Anastomotic leakage	18 (21%)		12		6	
Intrapelvic abscess	6 (7%)	1	4		1	
Intraperitoneal abscess	5 (6%)	1	0	3	1	
Rectovaginal fistula	4 (5%)		1		3	
Liver						
Bile leakage	7 (8%)	6	1			
Hepatic abscess	7 (8%)		5	1	1	
Liver failure	3 (3%)	1	1			1
Postoperative bleeding	1 (1%)				1	
Other organs						
Wound infection	25 (29%)	23	2			
Pleural effusion	12 (14%)	1		11		
Wound dehiscence	6 (7%)	3	2		1	
Enteroparesis	5 (6%)	5				
Postoperative delirium	4 (5%)	1	3			
Dysuria	4 (5%)		4			
Urinary tract infection	3 (3%)		3			
Pneumonia	2 (2%)		2			
Others	7 (8%)	1	4		2	

resection (n=4) or Hartmann's operation (n=1) were excluded from the analysis. Anastomotic leakage was significantly correlated with lateral lymph node dissection (p<0.01), primary site of rectum (p=0.01), duration of operation greater than 8 h (p<0.01), and amount of intraoperative blood loss (p=0.02). Neither serum levels of TP and ALB, steroid usage, nor neoadjuvant therapy showed correlation with occurrence of anastomotic leakage (data not shown). Multivariate analyses revealed operation time greater than 8 h (p<0.01) as the only independent predictive factor for anastomotic leakage after simultaneous resection of SCLM (Table 2). Extent of hepatectomy, timing of anastomosis and hepatectomy, and usage of Pringle maneuver did not correlate with occurrence of complication or anastomotic leakage.

Table 3 showed the rates of complication ≥ IIIa and anastomotic leakage according to operative procedures of the primary and hepatic resections which were performed in the same patient. Complication ≥ IIIa and anastomotic leakage were more frequently observed in patients with rectal resection; however, extent of hepatectomy did not seem to affect occurrence of complication ≥ IIIa or anastomotic leakage.

Hospitalization was significantly longer in the 55 patients with postoperative morbidity (32.2 days) than in the 31 patients without postoperative morbidity (17.6 days) (p<0.01). In addition, hospitalization was significantly longer in the 18 patients with anastomotic leakage (43.5 days) than in the 63 patients without anastomotic leakage (22.2 days) (p<0.01).

Survival

The overall survival rate after simultaneous resection for SCLM of the 86 patients was 61% at 3 years and 45% at 5 years, with MST of 47 months.

Discussion

For patients with resectable SCLM, both primary tumor resection and hepatectomy for liver metastasis could lead to long-term survival, with a 5-year survival rate of 23–37%. However, the optimal strategy, including surgical resection and perioperative treatment, remains controversial for resectable SCLM. In terms of surgical resection for SCLM, it has not been resolved whether simultaneous resection or staged resections would be preferable.

There are several rationales for simultaneous resection of SCLM. In simultaneous resection, the treatment strategy would become simpler. In the staged resections, a series of neoadjuvant chemotherapy or chemoradiotherapy, resection of primary tumor, chemotherapy between two operations, hepatectomy, and adjuvant chemotherapy could be the maximal total treatment for SCLM, while simultaneous resection could simplify and shorten the treatment schedule by eliminating one operation. Completion of the two resections and initiation of adjuvant chemotherapy occur earlier with simultaneous resection than with staged resections. Considering survival, comparable survival for simultaneous resection was shown in comparison with that for staged resections.[13] Furthermore, simultaneous resection could relieve patients from a considerable degree of mental and physical stress and decrease total treatment cost by preventing a second resection for hepatic metastases. Recent advances in colorectal and hepatic surgery have enabled simultaneous resection to be performed more safely. Martin et al. reported the safety and efficacy of simultaneous resection. By avoiding a second laparotomy, the overall complication rate was reduced, and length of hospital stay was shortened, with no change in operative mortality.[7,8]

However, at present, staged resections with initial resection of the primary tumor followed by hepatic resection have been frequently performed in patients with SCLM for several reasons.[4,5,9,10] First, the perioperative risk of staged resections has been thought to be less than that of simultaneous resection.[4,13,14] Sheele et al. reported 13 anastomotic leakages of 90 simultaneous procedures in their series, and two of them led to death.[4] Thelen et al. proposed the criteria for simultaneous liver resection according to the age and extent of liver resection, because death after simultaneous liver resection (n=4) occurred after major hepatectomies, and three of these four patients were 70 years of age or older.[15] Second, staged resections might offer a chance to evaluate liver or extrahepatic metastases between the two operations. Lambert et al. reported that staged resections of synchronous hepatic metastases with an interval of 3 to 6 months might allow occult disease to become clinically detectable and could potentially identify patients for whom a hepatic resection would offer no survival benefit.[10] Fujita recommended an interval resection to assess the metastatic status of the regional lymph nodes, because the presence of six or more lymph node metastases was an independent poor prognostic factor in patients with resected SCLM and a relative contraindication for hepatic resection.[9] Some authors proposed chemotherapy between primary tumor resection and liver resection to select patients that could benefit from hepatectomy.[13,16] Alternatively, a liver-first approach of doing liver resection first and primary resection second was newly proposed as a strategy for SCLM.[17,18] The liver-first approach might avoid needless radical colorectal surgery by confirming curability of hepatic metastases first and also might increase resectability compared with the ordinary staged resections especially in patients with progressive hepatic metastases.

Table 2 Correlation between anastomotic leakage and clinicopathological factors in patients who underwent simultaneous resection for SCLM

		Leakage (−) (n=63)	Leakage (+) (n=18)	Univariate analysis p value	Multivariate analysis p value, RR (95%CI)
Patient characteristics					
Median age (range) (years)		59 (40–85)	59 (41–73)	0.81	
Male/female		33/30	12/6	0.42	
BMI (mean±SD)		21.9±2.9	22.5±2.2	0.44	
Preoperative comorbidity					
Absent		44	12	0.78	
Present		19	6		
Primary colorectal tumor					
Site	Colon	42	6	0.01	N.S.
	Rectum	21	12		
Stenosis	Absent	56	0	0.34	
	Present	7	18		
Tumor size, mm		52.0	58.0	0.25	
pT stage	pT3	41	9	0.25	
	pT4	22	9		
pN stage	pN0	17	2	0.22	
	pN+	46	16		
Histology	Well, mod	60	15	0.12	
	Poor	3	3		
Liver metastasis					
Distribution	Unilobar	38	9	0.43	
	Bilobar	25	9		
Number of tumors (range)		2.3 (1–8)	2.6 (1–8)	0.57	
Tumor size, mm		47	33	0.06	
Operative factors					
Lateral lymph node dissection					
Absent		55	10	<0.01	N.S.
Present		8	8		
Diverting stoma					
Absent		48	11	0.24	
Present		15	7		
Liver resection					
Partial Hx, segmentectomy		51	16	0.72	
≥Lobectomy		12	2		
Timing of anastomosis					
Colectomy→anastomosis→Hx		20	4	0.20	
Colectomy→Hx→anastomosis		7	5		
Hx→colectomy→anastomosis		36	9		
Pringle maneuver					
Absent		10	1	0.44	
Present		53	17		
Operation time					
<8 h		53	8	<0.01	<0.01, 6.63 (2.09–20.9)
≥8 h		10	10		
Blood loss, g (range)		1,345 (162–6,000)	2,487 (430–6,560)	0.02	N.S.
Transfusion					
Absent		39	9	0.37	
Present		24	9		
Blood transfusion, ml		343	1,212	0.05	

RR relative risk, *CI* confidence interval, *Hx* hepatectomy, *N.S.* non-significant (p>0.05)