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疾病と治療II

消化器系／代謝・内分泌系／血液・造血器系／アレルギー／膠原病

総編集 松田 暉
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林 直子

New Integrated, Creative, Evidence-based

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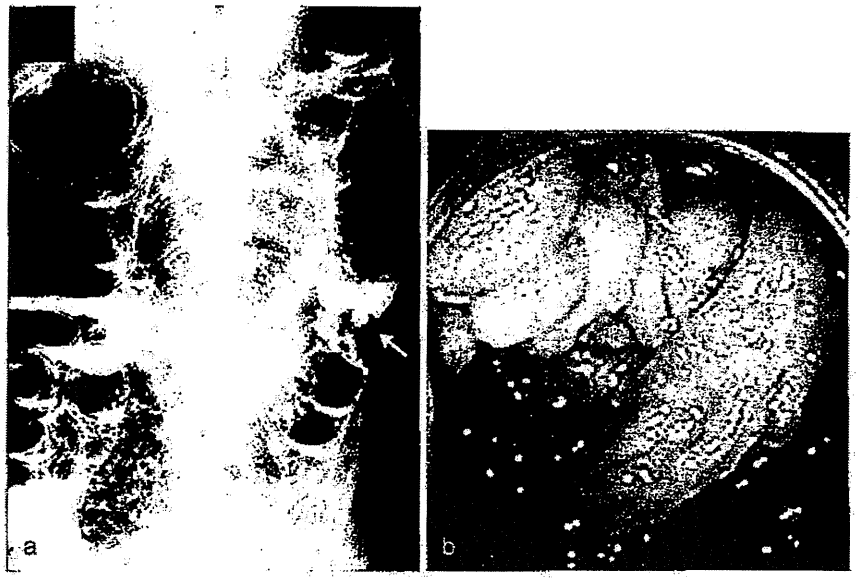

図 1　家族性大腸腺腫症の検査所見
a. 注腸造影検査にて，全大腸にびまん性に密生する微小ポリープを認める．下行結腸（矢印）には，進行大腸がんの合併による陰影欠損を認める．
b. 大腸内視鏡にて，多発する大小のポリープを認める．

◉診断のすすめ方

下痢，腹痛，血便などの症状で疑われるが，随伴病変によって発見される場合もある．

大腸のポリポーシスの検査として，注腸造影，大腸内視鏡検査を行う（図 1）．確定診断のためには，内視鏡検査下の生検病理組織学的検査が必須である．

ほかの消化管におけるポリープの存在診断のため，上部消化管内視鏡検査，小腸 X 線造影検査，小腸内視鏡検査などを行う．また，必要に応じて他臓器の合併症の検索が行われる．遺伝性を有する場合は，患者のみならず，家族も含めた遺伝子診断を考慮する．

◉主な治療法

FAP は放置すればほぼ 100％がん化をきたすと考えられており，患者への説明は社会的な問題も考慮したうえで，慎重に行う必要がある．がん化するまでに手術することが望ましく，予防的に全大腸切除を行うことが多い．

ポイツ・ジェガース症候群では，腸重積の原因となるような大きなポリープを内視鏡的に切除する．

V. 大腸がん

◉大腸がんとは

大腸がん（colon cancer）とは，結腸（盲腸，上行結腸，横行結腸，下行結腸，S 状結腸，直腸 S 状部）および直腸（上部直腸，下部直腸）の粘膜面より発生する上皮由来の悪性腫瘍の総称である．厚生労働省の「人口動態統計」によると，男女とも増加傾向が続いている．平成 19 年度の報告によると，悪性新生物による死亡者のうち，大腸がんは 20％を占めており，男性では第 3 位，女性では平成 15 年から胃がんを抜いて第 1 位である．好発年齢は 60 歳代である．直腸がん・結腸がんにおける罹患率・死亡率はいずれも男性に多い．

大腸の部位別では直腸がんがもっとも多く，大腸がん全体の 60％ほどだったが，近年ではその割合が約 40％と減少してきた．一方，S 状結腸がんが増加している．現在では直腸がんと S 状結腸がんだけで大腸がん全体の約 70％を占める．今後も大腸がんの増加が予想されるため，医療に携わるものにとって，より身近な疾患として理解を深める必要がある．

◉発症機序

大腸の発がんには，環境要因と遺伝的要因の

双方が関与するが，食生活などの環境要因や加齢の影響がより大きいとされる．近年，わが国において急速に大腸がんが増加してきたのは，食事の欧米化の影響が大きいと考えられる．高脂肪食は胆汁酸分泌を促進し，腸内細菌叢の変化により二次胆汁酸を増加させる．また，低繊維食は，便の通過時間を遅らせ，大腸粘膜への二次胆汁酸の曝露を増加させるとされる．大腸がん発生の危険因子には，食事のほかにアルコール，喫煙，肥満などがある．

大腸の壁の構造は，内側より粘膜層，粘膜筋板，粘膜下層，固有筋層（2層），漿膜下層，漿膜であり，大腸がんは粘膜から発生する（図1）．粘膜以外より発生する悪性腫瘍にはカルチノイド，悪性リンパ腫，悪性黒色腫，平滑筋肉腫などがあるが，その頻度はきわめて低い．大腸がんは前駆病変を経て発生すると考えられている．大腸粘膜上皮細胞のがん関連遺伝子に異常が蓄積し，いわゆる多段階発がんにより，大腸ポリープ（腺腫）を経て発がんすることが知られている（adenoma-carcinoma sequence，腺腫がん相関）．近年，腺腫以外の鋸歯状ポリープの一部からの発がんが指摘されており，また，前がん病変を認めず，正常粘膜から生じる例（*de novo* 発がん）も報告されている．

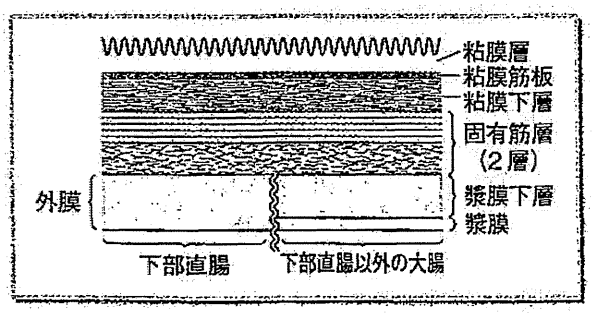

図1　大腸壁の構造

遺伝性大腸がんは5%以下と少ないが，家族性大腸腺腫症（FAP）とリンチ症候群（遺伝性非ポリポーシス大腸がん）が，発がん高危険群としてきわめて重要である．これらは大腸以外の臓器に発生する重複がんのハイリスク群としても注意が必要である．一方，潰瘍性大腸炎やクローン病などの炎症性腸疾患の長期経過例に大腸がんが発症しやすいことが知られている．

◉症状

大腸がんの早期には自覚症状に乏しいことが多いが，進行すると下血や，腹痛・嘔吐などの腸閉塞症状を呈するようになる．しかし，右側にできた大腸がんは管腔が広く，通過する腸内容も流動性なのでがんが大きくなるまで症状が出にくい．

◉大腸がんの分類

大腸がんの肉眼分類は，胃がんの分類を参考に作られ，表1に示すとおりである．しかし，進行がんはほとんど同じ形で，潰瘍限局型（2型）が多い．早期がんはがん浸潤が粘膜下層に留まるものと定義され，リンパ節転移の有無を問わない．したがって，早期がんでもリンパ節転移の有無によって治療法が異なる．早期がん（主として表在型）の肉眼形態も胃がんにならって表1に示すように細かく定義されているが，隆起型（I型：Ip，Isp，Is）のものが約70%を占める．

◉大腸がんの特徴

大腸がんは多発する傾向がある．大腸多発がんとは，大腸に原発性のがん腫が2個以上発生したものである．1年未満の期間に診断されたがんを同時性がんとし，大腸がん全体の7%を占める．1年以上の期間に診断されたがんを異時性がんとする．病理組織形態は高分化から

表1　大腸がん肉眼型分類

0型：表在型	0型（表在型）の亜分類
1型：隆起腫瘤型	I：隆起型　Ip：有茎性
2型：潰瘍限局型	Isp：亜有茎性
3型：潰瘍浸潤型	Is：無茎性
4型：びまん浸潤型	II：表面型　IIa：表面隆起型
5型：分類不能	IIb：表面平坦型
	IIc：表面陥凹型

［大腸癌取扱い規約，第7版補訂版，大腸癌研究会（編），9頁，金原出版，2009より転載］

表2 大腸がんの進行度分類

進行度	深達度	リンパ節転移	遠隔転移
0	粘膜まで	なし	なし
I	筋層まで	なし	なし
II	他臓器浸潤まで	なし	なし
IIIa	深達度に関係なし	N1まで	なし
IIIb	深達度に関係なし	N2, N3	なし
IV	深達度に関係なし	Nに関係なし	あり

N1：腸管傍リンパ節および中間リンパ節に転移3個以下
N2：腸管傍リンパ節および中間リンパ節に転移4個以上
N3：主リンパ節または側方リンパ節に転移を認める

[大腸癌取扱い規約，第7版補訂版，大腸癌研究会（編），16頁，金原出版，2009より一部改変して転載]

中分化腺がんがほとんどであり，ほかのがん腫に比べると比較的おとなしいがんといえる．

病期分類は，がんの壁深達度とリンパ節転移・遠隔転移によって決まる（表2）．手術後5年間，再発なく生存していればほぼ治癒したと考えられる．治療成績は病期分類と密接な関係があるが，遠隔転移がない病期IIIまでの治療成績はかなりよく，治癒切除例の累積5年生存率は，病期Iで90%，病期IIで80%，病期IIIaで70%，病期IIIbで56%であり，決して治癒が困難ながんではない．しかし，遠隔転移（病期IV）があると5年生存率は急激に低下し，10～20%となる．

●診断のすすめ方

◉スクリーニング検査

大腸がん検診として，一般的に便潜血検査が用いられるが，偽陽性率・偽陰性率がともに高く，検出率は低い．わが国では平成4年より40歳以上を対象に便潜血2日法により実施されているが，受診率は18%に留まり，要精検率は7%前後で推移している．要精検者のうち大腸がんが見つかるのは約2%である．

血液検査では，腫瘍マーカーとしてCEAとCA19-9が使用される．CEAとCA19-9は病期が進むに従って上昇するが，進行がんでも陰性の場合がある．また，炎症や喫煙でも陽性になることがあり，スクリーニングや早期診断には有用でない．

◉確定診断

大腸がんが疑われた場合，確定診断は大腸内視鏡検査における生検で得られる．内視鏡検査および注腸検査（またはCTコロノグラフィ）で腫瘍の局在・深達度診断を行うが，大腸多発がん，ポリープなどの併存病変の有無の検索も重要である．また，腹部骨盤・胸部CT検査などで肝臓・肺などへの遠隔転移の有無，リンパ節転移の有無，腫瘍の周囲臓器への浸潤の有無を検索する．直腸がんの骨盤内他臓器への進展，リンパ節転移の診断にはMRIも有効である．最近普及が進んだFDG-PET/CTも遠隔転移の全身検索などに有用なことがある．

また，手術を行うにあたり，胸部・腹部X線検査，心電図，肺機能検査，血液検査などにて全身状態をチェックする必要がある．

●主な治療法

手術療法（開腹，腹腔鏡補助下）が基本であるが，ほかに内視鏡的治療，化学療法，放射線療法などがあり，がんの進行度・患者の状況などに応じて種々に選択し，またこれらを組み合わせた集学的治療が行われる．この際，わが国では大腸がん研究会で編集された，大腸がん治療ガイドラインが1つの目安となる．

◉大腸がん治療の基本的な考え方

遠隔転移をきたしていない大腸がん治療の基本は手術療法であり，化学療法，放射線療法などの治療法に比較して治療効果がもっとも高い．基本的には腫瘍を含めた腸管の切除と，が

んの進展様式の1つであり予後因子としても重要な所属リンパ節の切除（郭清）を行う．

しかし，リンパ節転移の可能性がほとんどなく，腫瘍が一括切除できる大きさ（最大径2 cm未満）と部位にある早期がん（粘膜内がん・粘膜下層への軽度浸潤がん）の場合は，内視鏡治療で十分と考えられる．

◉内視鏡治療法

内視鏡治療法にはポリペクトミー，内視鏡的粘膜切除術（EMR）と内視鏡的粘膜下層剥離術（ESD）がある．

ポリペクトミー：病巣茎部にスネアをかけて高周波電流によって焼灼切除する方法であり，主として隆起性病変に用いられる．

EMR：粘膜下層に生理食塩水などを局注して病巣を挙上させ，ポリペクトミーの手技により焼灼切除する方法である．主として表面型腫瘍や大きな無形成病変に用いられる（☞38, 56, 81頁，『疾病と検査』「EMR」）．

ESD：病変周囲，粘膜下層にヒアルロン酸ナトリウム溶液などを局注して病巣を挙上させ，専用の電気ナイフで病変周辺の切開，粘膜下層の剥離を進める手技である．主として，EMRで一括切除できない大きな腫瘍が適応となるが，大腸のESDは手技の難易度が高く，合併症（穿孔）の危険性が高いので，現時点ではまだ一般的な治療法ではない（☞『疾病と検査』「ESD」）．

◉腹腔鏡補助下手術

腹腔鏡補助下手術とは，腹部を大きく開腹し直視下に手術を行う従来法に対して，腹腔鏡とよばれる内視鏡を用いて，二酸化炭素を用いた気腹（気体を腹腔内に充満させること）により手術の作業スペースを作り，細長い鉗子類を操作して，小さな術創でモニターを見ながら手術を行う方法である．この10年で低侵襲手術として大腸がんに対しても急速に普及した．術後の疼痛が軽く，術後の回復が早く，入院期間が短くて済む．また，創が小さいため美容上もすぐれており，術後の合併症の1つである癒着も少ないとされる．手術既往があり癒着が高度の場合や高度肥満の場合は腹腔鏡下手術が困難な場合があり，開腹手術に切り換えることもある．

◉大腸がんの治癒切除率

近年，大腸がんの治癒切除率は向上しているが，それでも約80％に留まる．治癒切除後にも約20％の再発がある．大腸がんの遠隔転移は，肝転移がもっとも多く，初診時において約10％ある．次いで，腹膜転移（5％），肺転移（1.5％），脳・骨・遠隔リンパ節転移など（0.1％未満）となる．同時性遠隔転移巣，ならびに原発巣がともに切除可能な場合には，原発巣の根治切除とともに遠隔転移巣の切除を考慮する．肝転移が切除できた場合の5年生存率は30～50％，肺転移が切除できた場合の5年生存率30～60％であり，切除による治療効果が望める．原発巣にしても遠隔転移巣にしても，根治的な切除不能な場合は全身化学療法が行われるが，局所化学療法，熱凝固療法，放射線療法が行われることもある．遠隔転移巣の切除は不能だが原発巣のみの切除が可能な場合には，臨床症状などから原発巣の切除が考慮される．

◉直腸がんにおける補助療法

直腸がんの手術において，術後の再発抑制や術前の腫瘍量減量，肛門温存を目的とした補助放射線療法が行われるようになってきた．術前に化学療法と組み合わせて放射線化学療法として行われることが多い．

化学療法には，術後再発抑制を目的とした補助化学療法がある．リンパ節郭清を含め，がんの遺残なく切除された症例に対し，予後を改善する目的で術後に実施される全身化学療法である．治療期間は6ヵ月が現時点では標準的であるが，至適投与方法，至適投与期間などに関して，現在多くの臨床試験で検討が行われている．

◉大腸がん手術の実際的手順

大腸がんの手術は次のように行われる．

①開腹（腫瘍の局在に応じた，術野操作の十分可能な皮膚切開）

②腹腔内の検索（腫瘍の局在，大きさ，リンパ節転移の程度，肝臓転移，腹膜播種の有無，他病変の有無などを確認）

③術式の選択（手術前の検査が十分行われていれば，術前に選択した術式と大幅に変わることは少ない）

④腸管の後腹膜よりの脱転（リンパ節郭清を先

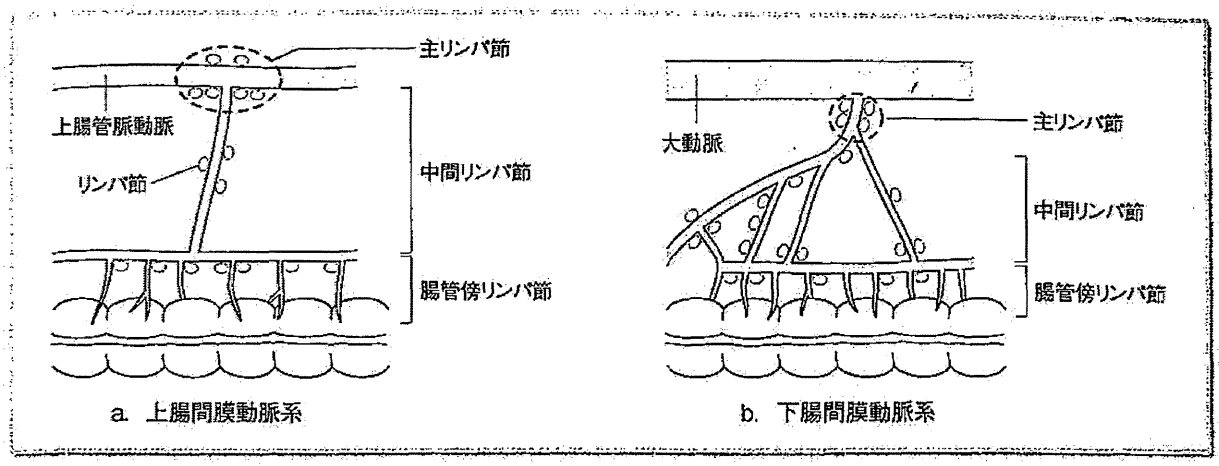

図2 リンパ節分類の基本

[大腸癌取扱い規約，第7版補訂版，大腸癌研究会（編），44頁，金原出版，2009より転載]

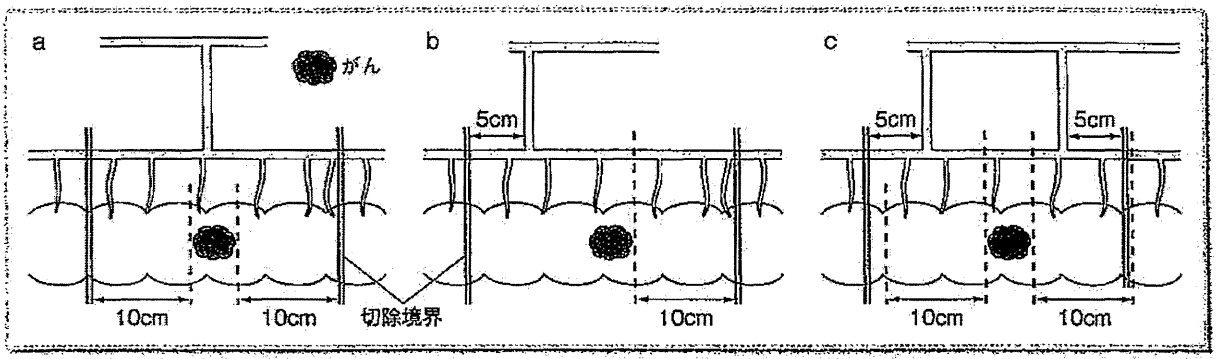

図3 結腸がんの腸管の切離範囲

[大腸癌取扱い規約，第7版補訂版，大腸癌研究会（編），45-46頁，金原出版，2009より改変して転載]

行する場合もある）

⑤リンパ節郭清（血管処理を先行し，リンパ節を含む腸間膜を郭清する）

⑥腸管の切除により，腫瘍と郭清したリンパ節を一続きに摘出

⑦腸管の吻合（人工肛門を造設し，吻合を要さない場合もある）

⑧腹腔内の洗浄，止血，異物の有無の確認（必要であればドレーンの留置）

⑨閉腹

以下に，結腸がん，直腸がん，それぞれの手術方法について具体的に述べる．

1. 結腸がんの手術

◉リンパ節の郭清範囲

リンパ流を考慮し，リンパ節の郭清範囲を決定する．結腸がんのリンパ流は，支配動脈に沿って，その根部へ向かう中枢方向（主リンパ節，中間リンパ節）と，腸管軸に沿った方向（腸管傍リンパ節）の2つの流れがある（図2）．転移リンパ節は支配動脈で囲まれる領域のみに存在し，腸管軸方向では腫瘍から5 cm以内に存在する．したがって，進行結腸がんの3群までの郭清範囲は，中枢方向では主リンパ節と中間リンパ節を，腸管軸方向では，腫瘍より10 cm離しての扇型切除が原則である（図3a）．ただし，腫瘍よりもっとも近い支配動脈より5 cm外側まで切離する（図3b）．腫瘍より10 cm以内に支配動脈が2本ある場合は，それぞれの起始部より5 cm外側を切離する（図3c）．

◉手術法

結腸の支配動脈は，回結腸動脈，右結腸動脈，中結腸動脈，左結腸動脈，S状結腸動脈がある．がん腫の局在場所により，回盲部切除術，（拡大）右半結腸切除術，横行結腸切除術，（拡大）左半結腸切除術，S状結腸切除術などが行われ，切除範囲，吻合法は図4に示したとおりである．結腸は長さが1 m以上もあり，数十cm切

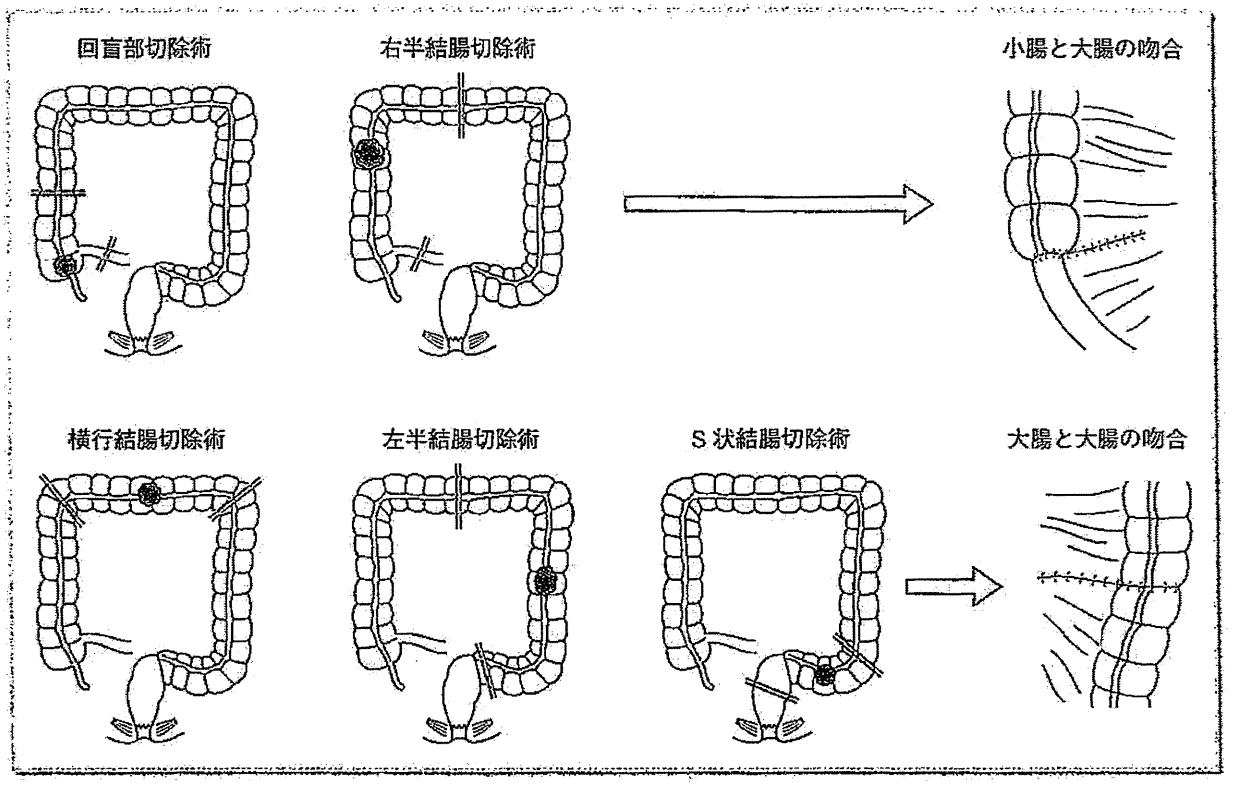

図4　結腸がんの手術法

除しても機能的にはほとんど問題ない．

◉術後の合併症

結腸がんの手術での合併症は少ない．1994年の大腸がん全国登録データによると0.8%である．頻度は，創感染，腸閉塞，縫合不全，出血の順に多いが，そのほか手術共通の合併症としては，肺炎，深部静脈血栓症などがある．

2. 直腸がんの手術

◉リンパ節の郭清範囲

直腸がんのリンパ節の郭清範囲は，図5に示すごとく，中枢方向は下腸間膜動脈根部が主リンパ節，上直腸動脈に沿う領域が中間リンパ節となる．下部直腸がんでは，リンパ流として側方の腸骨動脈領域に向かうもの（主リンパ節に相当）を考慮する必要がある．腸管傍リンパ節としては直腸間膜ごと間膜内のリンパ節を切除すること（直腸間膜全切除）が，局所再発の頻度を下げるために重要である．肛門側の腸管切除は上部直腸がんでは3 cm，下部直腸がんでは2 cmで十分である．口側の切除腸管は，最下S状結腸動脈流入点まで，あるいは10 cmの長いほうを選択すれば十分と考えられる．

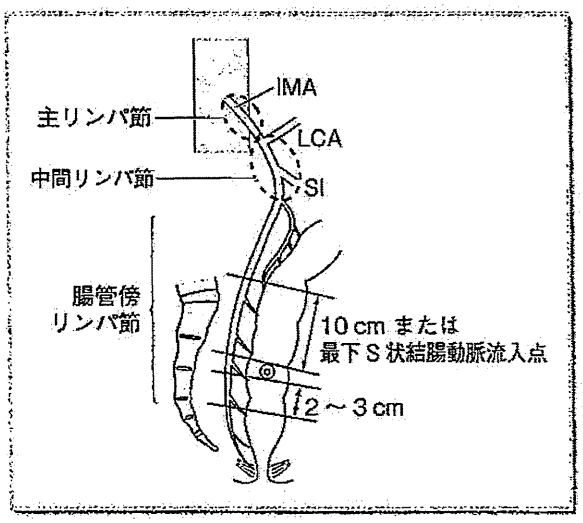

図5　直腸がんのリンパ節
側方リンパ節は下部直腸がんの主リンパ節に相当する．

◉手術法

直腸がんの手術の種類は図6に示すとおりである．腸管の吻合を行って，永久人工肛門を避ける手術を前方切除という（背中側から直腸を切除する方法を後方切除（経仙骨式切除）とよぶのに対応する）．永久人工肛門を造設する手術は，マイルス（Miles）手術（直腸切断術）とハルトマン（Hartmann）手術である．

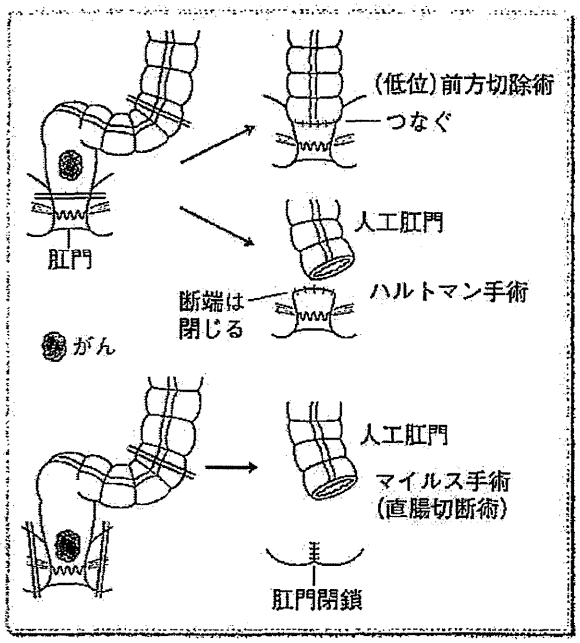

図6 直腸がんの手術法

器械吻合を用いることにより低位で吻合することができるようになり，以前より永久人工肛門造設件数が減っている．前方切除のうち，吻合が腹膜反転部より低位となる場合には低位前方切除術というが，さらに低位の肛門管内で吻合がなされた場合には超低位前方切除とよぶ．一般的ではないが，内肛門括約筋を切除し，肛門に手縫い吻合することにより，さらに低位の直腸がんに対して肛門温存手術ができるようになってきた．吻合が低位になる場合には，術後の縫合不全による再手術を避ける目的で，原発巣手術時に，双口式人工肛門を回腸末端部に造設する場合がある．術後縫合不全のないことが確認された適当な時期（1から6ヵ月後）に人工肛門閉鎖の手術を行う．

◉手術後の機能障害，合併症

手術前後の経過は結腸がんとほぼ同様であるが，合併症はやや多く，とりわけ縫合不全は結腸がんの約10倍となり，吻合が肛門に近づくほど頻度が高くなる．機能的な問題として，排尿障害，排便障害，性機能障害を生じることがある．性機能障害（勃起障害・射精障害），排尿障害（神経因性膀胱）は，自律神経である腰内臓神経から下降する上下腹神経，これに引き続く下腹神経，下部直腸の左右に存在する骨盤神経叢を術中に切除することがあるために生じる．そのほか，直腸が短くなり，便の貯留能がなくなるため，排便回数が増えるという問題点がある．一般的には，肛門に近いところで吻合するほど顕著となり，1日に数十回に及ぶこともある．半年から1年経つと，大概は1日に数回のレベルまで落ち着いてくる．

（冨田 尚裕）

W. 虫垂炎

●虫垂炎とは

虫垂炎（appendicitis）とは，虫垂の非特異的化膿性炎症であり，急性腹症でも頻度の高い疾患である．虫垂の内腔が糞石やX線検査時の造影剤，食物残渣などによって閉塞し，そこに腸内細菌が感染して発症する．処置の遅れにより重篤となる場合があり，素早い対応が要求される．

◉症状

典型的な症状は，食欲不振，心窩部痛，悪心・嘔吐で始まり，数時間経て右下腹部に限局した疼痛へ移行する．37～39℃の発熱を伴うことが多い．一般に，腸管は麻痺性となり排ガス停止がみられることが多い．小児，老人ではこのような典型的症状が出ない場合もある．

◉分類

病理学的特徴により以下の3つのタイプに分類される．

①カタル性虫垂炎：炎症が粘膜層に限局している
②化膿性（蜂巣炎性）虫垂炎：全層に炎症が生じる
③壊疽性虫垂炎：粘膜面や全層に壊死が生じる

これらの中でも，壊疽性虫垂炎は穿孔しやすく重篤化しやすい．

●診断のすすめ方

虫垂炎における診療の流れを図1に示す．

a. 身体所見

虫垂炎に関する圧痛点は多く知られている（図2）．これらのうち，マックバーネー（Mcburney）点とランツ（Lanz）点はとくに診断意義が高く有用である．

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SURGERY TODAY

Review Articles

Strategies for Treating Liver Metastasis from Gastric Cancer

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Abstract
The prognosis of patients with liver metastasis from gastric cancer is dismal. This article reviews the characteristics of gastric cancer metastasizing to the liver, and multimodality of treatments. Differentiated adenocarcinoma, poorly differentiated adenocarcinoma with a medullary growth pattern, and special types, including endocrine carcinoma and hepatoid carcinoma, are likely to metastasize to the liver. The overexpression of growth factors or adhesion molecules is clinically significant for liver metastasis. Surgery for liver metastases arising from gastric adenocarcinoma is reasonable if a complete resection seems feasible after careful preoperative staging. A hepatic resection should always be considered as an option for gastric cancer patients with hepatic metastases. Newer generation cytotoxic agents such as S-1, irinotecan, and taxanes show promising activity for patients with metastases. Adjuvant chemotherapy or molecular targeted therapy will provide significant benefits to patients in the future.

Key words Gastric cancer · Hepatic resection · Liver metastasis · Adjuvant chemotherapy

Introduction

Gastric cancer was the fourth most common malignancy in the world in 2007, with an estimated 1 million new cases.[1] It is the second leading cause of cancer death in men and the fourth among women. In Japan, it is second only to lung cancer among deaths due to cancer.[2] As adequate local control is essential for the treatment of gastric cancer, the standard of care for curable gastric cancer in eastern Asia and the United States is either gastrectomy with D2 lymphadenectomy and without postoperative chemoradiation or D0 or D1 gastrectomy with postoperative chemoradiation.[3–7] However, liver metastasis is found in 4%–14% of patients with primary gastric cancer,[8–11] which is often associated with extrahepatic disease such as peritoneal dissemination, lymph node metastasis, and direct cancer invasion of other organs. Gastric cancer with liver metastasis is a noncurable, fatal disease with a 5-year survival of less than 10%. This article reviews the characteristics of gastric cancer with liver metastasis and the up-to-date treatment of hematogenous metastasis.

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Characteristics of Gastric Cancer with Liver Metastasis

Three histological subtypes of gastric cancer are likely to metastasize to the liver: differentiated adenocarcinoma, poorly differentiated adenocarcinoma, and a special type including endocrine carcinoma and hepatoid carcinoma.[12–15] The differentiated type grows in a papillary or tubular pattern. The poorly differentiated type exhibits a medullary growth pattern. Gastric hepatoid adenocarcinoma is histologically similar to hepatocellular carcinoma.[15] These subtypes have unique characteristics, but share common pathological features such as scant fibrous stroma and abundant tumor blood vessels.[11] The clinicopathological features of gastric cancer with liver metastasis are an expansive pattern of growth, prominent vascular involvement, and a high rate of lymph node metastasis.[16]

Some biological characteristics have been reported to be correlated with liver metastasis. The overexpression of growth factors (c-Met,[17] vascular endothelial growth factor [VEGF][18]) or adhesion molecules (intercellular adhesion molecule 1 [ICAM-1][19] or LFA-3[20]) are clinically significant for liver metastasis.

The *c-Met proto-oncogene* encodes the c-Met receptor, which is a 190-kDa heterodimeric glycoprotein with

two subunits linked by disulfide bonds: a 50-kDa extracellular α-chain and a 145-kDa transmembrane β-chain with a cytoplasmic tyrosine kinase domain.[21] When the ligand of c-Met, hepatocyte growth factor (HGF), binds to c-Met receptor, the tyrosine kinase of the β-chain is activated and the signal is transmitted.[22] c-Met is overexpressed in 18%–68.8% of gastric cancer tissues, and there is a higher degree of c-Met protein expression in carcinoma cells in stage IV gastric cancers with liver metastasis in comparison to that in cancers without liver metastasis.[17] These observations were confirmed at the mRNA level by a semiquantitative reverse transcription–polymerase chain reaction (RT-PCR) analysis. Hepatocyte growth factor is expressed in both carcinoma and stromal cells in gastric cancers.[17] Hepatocyte growth factor produced by cancer cells may induce the proliferative activity of cancer cells in an autocrine fashion. Furthermore, HGF has angiogenic activity that stimulates the proliferation of endothelial cells and is capable of degrading extracellular matrix proteins.[23] The degradation of the basement membrane or extracellular matrix is essential for tumor invasion, and angiogenesis is deeply involved in this process. These observations suggest that HGF may participate in the process of tumor invasion or metastasis through paracrine or autocrine mechanisms. The c-Met/HGF system seems to be more active in the gastric cancer group with liver metastasis.

Vascular endothelial growth factor is a dimeric, heparin-binding glycoprotein that functions as a potent mitogen of vascular endothelial cells, thus providing an opportunity for their migration and organization for the neovascularization of micrometastases.[24] The immunohistochemical expression of VEGF in gastric cancer is associated with increased microvessel density, lymphatic and venous invasion, and lymph node and liver metastases.[18]

Intercellular adhesion molecule-1 and -2 are cell adhesion molecules identified as ligands of lymphocyte function-associated antigen-1 (LFA-1), which is expressed by lymphocytes. These proteins are expressed by various cells, such as vascular endothelial cells, fibroblasts, and epithelial cells.[25–27] Intercellular adhesion molecule-1 is a glycoprotein with an extracellular region that has an immunoglobulin-like structure and, thus belongs to the immunoglobulin superfamily.[28] Its expression is enhanced by cytokines such as interleukin (IL)-1 and interferon (IFN)-γ.[27] Intercellular adhesion molecule-1 is a cell adhesion molecule that takes part in the destruction of cancer cells by immunocytes. Overexpressed ICAM-1 may be released from cells in a local cancer cell nest and enter the serum as soluble ICAM-1 (s-ICAM-1), which suppresses immunocytes by binding to LFA-1. The rate of ICAM-1 expression increases slightly according to the stage and its expression is higher in advanced cancer.[19] In addition, the rate of ICAM-1 expression is markedly correlated with metastasis to the lymph nodes and the liver. ICAM-1 is overexpressed in cancer cells and released as s-ICAM-1, which promotes hematogenous metastasis by suppressing local anticancer immunity. The serum s-ICAM-1 level may be useful for monitoring hematogenous metastasis during postoperative follow-up, and the development of an absorption technique for s-ICAM-1 may reduce postoperative hematogenous metastasis.

Intercellular adhesion molecule-1 and LFA-3 are adhesion molecules and members of the immunoglobulin superfamily that appear to be essential for the interactions of T cells with other immune cells and their targets by mediating strong adhesion.[29] A higher percentage of lymphocytes in hepatic sinusoids in normal livers express LFA-1, MAC-1, ICAM-1, and LFA-3 on their surface than peripheral blood lymphocytes,[30] and both ICAM-1 and LFA-3 are strongly expressed in hepatocytes and other target structures from patients with inflammatory liver diseases.[31] Primary tumors and metastases in draining lymph nodes demonstrate a broad range of LFA-3 expression. In contrast, distant metastases (liver and peritoneum) have uniformly high frequencies of LFA-3-positive cells, thus suggesting a selective advantage for these cells in the establishment of distant metastases.[20]

The molecular mechanism of liver metastasis still remains essentially unknown. Experimental analyses of liver metastasis using gastric cancer cell lines or animal models are therefore important to reveal the mechanism of hematogenous metastasis and to develop new therapeutic strategy. Most gastric cancer cell lines were derived from ascites or lymph node metastasis, and there are cell lines derived from liver metastasis.[32,33] Both genetic alterations and cellular adjustments to the microenvironment are required for hepatic metastasis in gastric cancer.[34] The parental YCC-16 shows multiple metastases, whereas the liver metastatic clones metastasize to the liver only. In vertebrates, dystroglycan is generated from a single gene (DAG1), which is located on the chromosome 3p. YCC-16 presents the lowest DAG1 expression level while the cell line from the orthotopic primary tumor (S1L0) presents the highest. The DAG1 expression level in the liver metastatic clones increases gradually with passages.

Surgery for Liver Metastasis

A surgical resection of liver metastasis from gastric cancer is rarely indicated, because liver metastasis is often associated with extrahepatic disease, such as peritoneal dissemination, lymph node metastasis, and direct

Table 1. Results of hepatic resections for metastasis from gastric cancer

First author[Ref]	Year	No. of pts. with liver metastasis	No. of pts. who underwent hepatic resection	Median survival time (months)	5-Year survival after resection	Prognostic factors by multivariate analysis	Indications for surgery
Ambiru[40]	2001	—	40	12	18%	Synchronous metastasis	Metachronous metastasis
Okano[9]	2002	90	19 (21.1%)	21	34%	Multiple metastases Synchronous metastasis	Solitary metastasis Metachronous metastasis
Shirabe[36]	2003	—	36	NA	26%	Vessel invasion Number of metastasis	No vessel invasion One or two metastases
Sakamoto[11]	2007	182	37 (20.3%)	31	11%	Bilobar metastasis Tumor diameter ≥4 cm	Unilobar metastasis Tumor diameter <4 cm
Koga[38]	2007	247	42 (17.0%)	34	42%	Multiple metastases Serosal invasion	Solitary metastasis No serosal invasion
Cheon[41]	2008	58	22[a] (37.9%)	17	23%	Multiple metastases ($P = 0.0519$)	Solitary metastasis

NA, not assessed
[a] Patients who underwent a combined curative resection of gastric cancers and hepatic metastases

cancer invasion of other organs.[13] In contrast to colorectal cancer, the vast majority of patients with gastric cancer and liver involvement may reflect generalized disease. Selected patients accounting for one-fifth of all cases with liver metastasis can undergo hepatic resection[11] (Table 1). The survival rate after hepatectomy is rather unsatisfactory, because two-thirds of the patients develop intrahepatic recurrence.[11] This high recurrence rate within 2 years of the surgery might suggest the presence of occult intrahepatic metastases even at the time of the hepatectomy. There have so far been few reports of a repeat hepatectomy resulting in favorable outcomes.[10]

The significant prognostic factors are the stage of the primary gastric cancer, number of liver metastases, timing of the hepatectomy, and the surgical margin.[9,11,35–40] Ochiai et al.[37] suggested that a hepatic resection should be attempted in patients with synchronous or metachronous metastases if there is no serosal invasion by the primary gastric tumor, and if the primary tumor has neither venous nor lymphatic invasion in the case of metachronous metastases. Solitary metastases from gastric cancer are recommended for surgical treatment.[9,38] Sakamoto et al.[11] noted that unilobar metastasis and/or tumors less than 4 cm in diameter may be indicated for surgical resection. Furthermore, synchronous metastasis is not a contraindication for hepatectomy. As for surgical margin, some[39,40] concluded that positive surgical margins should be avoided, and others[11,41] reported that an extensive safety resection margin may not be essential for better outcomes of hepatic resection in gastric cancer. Cheon et al.[41] reported that the survival rates after curative intent do not differ between curative and palliative resections. At present, surgery for liver metastases arising from gastric adenocarcinoma is reasonable if a complete resection seems feasible after careful preoperative staging. A hepatic resection should be considered as an option for gastric cancer patients with hepatic metastasis.

Recurrent tumors usually develop in the liver following a hepatic resection for gastric metastases (62%–79%),[11,41] thus indicating that the remaining liver should be a focus for postoperative monitoring. A sensible strategy for improving survival would be close observation for a second relapse in the liver and adjuvant chemotherapy after surgery. The efficacy of adjuvant chemotherapy after resection of liver metastases has not been fully evaluated. A second hepatic resection is not usually selected for most recurrent intrahepatic metastases but systemic chemotherapy may be administered.[7]

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a popular alternative to surgery for tumor ablation due to its safety, availability, and wide applicability to primary or secondary hepatic malignancies.[42,43] Yamakado et al.[44] reported a prospective study that evaluated the efficacy of hepatic arterial infusion chemotherapy (HAIC) with use of an implanted port followed by radiofrequency (RF) ablation for the treatment of liver metastasis of gastric cancer. Seven patients without extrahepatic metastasis were enrolled. The maximum tumor size was less than 3 cm in one patient and 3.2–6.0 cm in the other six patients (mean, 4.4 ± 1.5 cm). The maximum tumor size was reduced to 3 cm or less (mean, 2.4 ± 0.4 cm; $P < 0.03$) after HAIC in all patients. Radiofrequency ablation was performed for all residual liver tumors, resulting in

complete tumor necrosis, with a median survival time of 16.5 months. The complementary role of the radiofrequency is recommended in the palliative treatment of the hepatic metastases of advanced gastric cancer that are difficult to treat surgically.[45] The size of the hepatic metastasis is the most important factor in determining whether complete local ablation can be achieved.[43] In general, lesions measuring less than 2.5 cm in diameter have a greater than 90% chance of being destroyed, and less than 50% of tumors measuring greater than 5 cm are likely to be completely ablated.[42] Gannon and Curley[46] recommended not treating tumors >5 cm in maximal diameter with RFA. With improvements in ablation techniques and instruments, the number and extent of RFA treatments is increasing.[47] However, the efficacy, indications, and limitations of this therapy for liver metastasis from gastric adenocarcinomas have not yet been studied in a large series of patients.

Systemic Chemotherapy for Liver Metastasis

The standard treatment regimen for patients with unresectable gastric cancer was a matter of debate for a long time. S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine (CDHP), and potassium oxonate in a molar ratio of 1:0.4:1.[48] Phase II studies of S-1 have yielded responses of 44%–54% in patients with advanced gastric cancer,[49,50] and in Japan, S-1 is mainly used as the first-line treatment for this type of cancer. The response rates for liver metastasis in these phase II studies are 25%–31%.[49,50] A phase III study conducted by the Japan Clinical Oncology Group (JCOG), study 9912, revealed that S-1 alone is no worse than fluorouracil alone.[51] In this study, irinotecan plus cisplatin was no better than fluorouracil alone. However, in subgroup analyses, the effect of irinotecan plus cisplatin on progression-free survival and overall survival was greater in patients with target lesions, such as lymph node metastases or liver metastases, than in those without target lesions. In addition, a trial of S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial) verified that the median overall survival was significantly longer in patients assigned to S-1 plus cisplatin (13.0 months) than in those assigned to S-1 alone (11.0 months).[51] This phase III trial identified S-1 plus cisplatin as one of the standard first regimen for advanced gastric cancer in Japan. In exploratory subgroup analyses using a Cox proportional-hazards model, the effect of S-1 plus cisplatin on overall survival was greater in patients with peritoneal metastasis than in those without peritoneal metastasis, and also in patients without target tumors than in those with target tumors.[52] A randomized phase III study of S-1 plus irinotecan versus S-1 alone (GC0301/TOP-002)[53] failed to prove the superiority of S-1 plus irinotecan to S-1 alone. The subgroup analysis of this study has not been disclosed. A phase III study of docetaxel and S-1 versus S-1 (JACCRO GC-03) is ongoing to determine the optimal combination.[54] A phase II study of docetaxel and S-1 combination therapy revealed that the response to docetaxel-S-1 was not affected by the type of organs involved or the histologic tumor type. The highest overall response rates among the metastatic sites were observed for liver (64.7%), locoregional lymph node (60.0%), and peritoneum (60.0%).[55] Newer generation cytotoxic agents such as S-1, irinotecan, and taxanes show promising activity for patients with metastatic gastric cancer. These agents will likely be evaluated in the future for their role as adjuvant and neoadjuvant therapy. The systemic or local control of the disease may give patients various chances to undergo curative surgery.

Elsewhere, triplet therapies are standard, such as docetaxel and cisplatin plus fluorouracil (DCF) in the United States,[56] or epirubicin and cisplatin plus fluorouracil (ECF) or epirubicin and oxaliplatin plus capecitabine (EOX) in Europe.[57] The efficacy of these therapies for liver metastases has not been reported. In Korea, cisplatin plus oral capecitabine (XP) is also reported to be recommended for advanced gastric cancer.[58]

Hepatic Arterial Infusion

Regional hepatic arterial infusion (HAI) of chemotherapy takes advantage of the first-pass effects of cytotoxic agents, delivering higher local drug concentration to unresectable liver tumors with fewer significant systemic side effects.[59] There have been few reports of hepatic arterial infusion for patients with liver metastases of gastric cancer.[60–63] In 1990s the response rate of HAI of MMC and cisplatin was 73% (17/23), and the median survival period was 11.8 months.[60] In an earlier preliminary phase II study performed by Arai et al.,[61] a high response rate of 73.3% (22 of 30 cases) was achieved by HAI therapy using 5-fluorouracil (5-FU), doxorubicin and mitomycin-C (MMC; FAM regimen), or 5-FU, epirubicin, and MMC (FEM regimen) in patients with hepatic metastases of gastric cancer. The multicenter phase II study evaluated the efficacy of the FEM regimen showed a response rate of 55.6% (35/63) and the mean 50% survival was 10.5 months.[63] However, most responders died due to the progression of extrahepatic lesions.

To enhance the effectiveness of regional treatment in patients with liver carcinoma, cytotoxic drugs may be

combined with alternative therapeutic strategies such as partial vascular blockade using degradable starch microspheres (DSM).[64] When DSM combined with a cytotoxic drug are infused through the hepatic artery, the steep drug concentration gradient to the tumor tissue results in higher tissue drug concentrations which may elicit an increased antitumor response. Hirasawa et al.[65] reported the effects of transcatheter arterial chemoembolization (TACE) using DSM in patients with hepatic metastases from gastric cancer after prior systemic chemotherapy. Infusion of epirubicin hydrochloride (40–70 mg/body) following arterial chemoembolization with DSM and mitomycin C (4–12 mg/body) was administered. The response rate was 62.5% (5/8) and the median survival time was 36.1 months. After the progression of the disease following systemic chemotherapy, HAI is another treatment for the patients with liver metastasis only.

Tumor Markers

The prevalence of positive tumor markers among gastric cancer patients selected for surgical resection is low, and when positive, provides little prognostic value.[66,67] The commonly used markers in gastric cancer are carcinoembryonic antigen (CEA)[68] and sialyl Lewis^a antigen (CA19-9).[69] A high percentage of CEA-positive tumors are noted in differentiated gastric cancers.[70] The preoperative level of CEA is strongly correlated with clinical estimation of tumor mass and progression of the disease.[71] Ishigami et al.[72] preoperatively estimated the levels of CEA and CA19-9 in patients with gastric cancer. The rates of CEA (≥5 ng/ml) and CA19-9 (≥37 U/ml) were 19.5% and 18%, respectively. The level of serum CEA and CA19-9 significantly correlated with depth of invasion, hepatic metastasis, and curativity. CA19-9 may be especially useful as a marker for peritoneal recurrence of gastric cancer, and CEA for recurrence to the liver.[73] Korenaga et al.[74] reported that CEA doubling time predicts life expectancy in patients with adenocarcinoma of the gastrointestinal tract. Positive CEA suggests recurrence to the liver. An RT-PCR analysis of CEA mRNA in the peripheral blood seems to be a promising tool for the early detection of micrometastatic circulating tumor cells in gastric carcinoma patients.[75]

There are some reports that α-fetoprotein (AFP)-producing gastric cancers are associated with a poor prognosis with lymphatic and venous microinvasion of the gastric wall, and high rates of liver metastasis, of both the synchronous and metachronous types.[76,77] There is limited information on the cellular or molecular characteristics of AFP-producing gastric cancers. c-Met overexpression is more frequently observed in AFP-producing gastric cancers than those not producing AFP.[78] The c-Met proto-oncogene encodes the c-Met receptor which regulates cell proliferation or migration,[79] and HGF has been identified as its ligand.[80] α-Fetoprotein-producing gastric cancer cells with higher c-Met expression grow more progressively in response to HGF, which is abundantly produced within cancer tissue. α-Fetoprotein-producing gastric cancers have a high proliferative activity, weak apoptosis, and rich neovascularization.[81] α-Fetoprotein-producing gastric cancers arise as an aggressive clone with extensive loss of heterozygosity (LOH) and high fractional allelic loss.[82] For informative cases, LOH is most frequently detected on 17p (100%), followed by 13q (88%), 3p (87%), 5q and 9p (80%), 11q (70%), 18q (58%), 16q (53%), and 8p (50%). The presence of heterogeneous patterns of LOH suggests that the AFP-producing carcinoma foci might evolve through genetic progression and/or genetic divergence. It is interesting to note that the loci of 13q that are commonly deleted in AFP-producing gastric carcinoma are also frequently deleted in hepatocellular carcinoma, which often presents with raised serum AFP values.

Sialyl Lewis^a (CA19-9) and sialyl Lewis^x antigens (SLX) may play a role in tumor metastasis by serving as functional ligands in the cell adhesion system.[80] An elevated preoperative serum SLX level is a predictor of poor outcome after a resection for gastric cancer, and a logistic regression analysis revealed that a high serum SLX level is an independent predictor of liver metastasis.[83]

Sialyl Tn antigen (STN) is a cell-membrane-bound mucin-like carbohydrate structure that is sometimes expressed in solid tumors because of blocked synthesis of the core carbohydrate chain of mucin-like structures.[84] Preoperative high serum levels of STN predict both liver metastasis and poor prognosis after a resection for gastric cancer.[85,86]

Gastric cancer metastasized to the liver is found to overexpress HER2 at a significantly higher incidence (65%) than primary gastric cancers (38%).[87] All these gastric cancer liver metastasis cell lines are highly sensitive to gefitinib, a specific inhibitor of EGFR tyrosine kinase (Iressa) rather than anti-HER2 antibody trastuzumab (Herceptin), whereas most of the HER2 low-expressing lines are not. The antitumor effect of gefitinib is due to the effective inhibition of HER2-driven constitutive activation of phosphatidylinositol-3-kinase (PI3K)/Akt pathway, and the acquired resistance to gefitinib is due to the constitutive activation of the Ras/MAPK pathway in compensation for the PI3K/Akt pathway.[87] Gastric cancer liver metastasis with HER2 overexpression could be a potential molecular target for gefitinib and trastuzumab.

Conclusions and Future Prospects

The optimal treatment of gastric cancer with liver metastases without peritoneal dissemination or other distant metastases remains a matter for debate. Surgery for liver metastases from gastric cancer may be indicated if a complete resection seems feasible after careful preoperative staging. Synchronous metastasis is therefore not a contraindication for a hepatectomy.

The preliminary results of a large neoadjuvant chemotherapy study have demonstrated the efficacy of this approach with tumor downstaging and increase in the curative R0 resection rate. Major advances in the treatment of gastric cancer have occurred during the past several years and have improved the care of patients with this form of tumor.

An improved understanding of the biological characteristics, such as the expression of growth factors or adhesion molecules including signal pathways in gastric cancer, will assist in the development of new targeted therapies and perhaps best define those patients with potentially chemosensitive tumors. Therefore, multimodality therapies and strategies are necessary for patients with liver metastases.

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The impact of a high-frequency microsatellite instability phenotype on the tumor location-related genetic differences in colorectal cancer

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Abstract The purpose of this study was to evaluate the genetic background of colorectal cancer according to the tumor site, and to investigate the impact of the genetic features regarding the lesion location of colorectal cancer. Microsatellite instability (MSI), DNA index, and the mutation and loss of heterozygosity of the *TP53* gene were systemically examined in 180 Japanese colorectal cancer cases. The correlation between these genetic features and clinicopathologic factors was analyzed. A logistic regression was undertaken to analyze the association between genetic features and tumor locations. The data demonstrated location-related genetic differences in colorectal cancer. The proximal subset was distinct in patterns of genomic instability and *TP53* gene defects. The genetic features of distal colon cancers paralleled those of rectal cancers. Intriguingly, a multivariate analysis implicated MSI as the only factor significantly associated with tumor location. When MSI tumors were excluded, the statistical association between tumor location and alternations in the DNA index and *TP53* vanished. The location-related differences of colorectal cancer were derived from the unequal distribution of the MSI tumors. On the other hand, the microsatellite stable colorectal cancers were genetically homogeneous regardless of the tumor location. Therefore, instead of tumor location, microsatellite status should be a major focus for the study of colorectal cancers in the future.

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in Western developed countries, and ranks the first when smoking-related cancers are excluded. According to the GLOBOCAN database (http://www.iarc.fr/), the incidence of CRC in Japan has dramatically increased during the past 60 years. The age-standardized rate of CRC in Japan is similar to that in North American and Western European countries [1,2].

The colonic and rectal subdivision of CRC is simple and practical, thus is applied by most cancer database registries [3]. On the other hand, many studies have indicated that cancers from the proximal and distal subset of the large bowel, separated by the splenic flexure, differ in genetic characteristics and clinicopathologic features [4]. Therefore, it is crucial to determine whether the tumor location of CRC should be a major concern, which will profoundly affect both clinical practice and the field of research.

Genomic instability is a defining characteristic of most human cancers [5]. Two patterns of genetic aberrations, chromosomal instability (CIN) and microsatellite instability (MSI), reveal the existence of at least two independent pathways for the tumorigenesis of CRC [6]. A high frequency MSI (MSI-H), which is derived from aberrations in the DNA mismatch repair system, occurs in about 15% percent of CRC [7]. The MSI-H cancers usually have a diploid or near-diploid chromosomal content and are predisposed to mutations at the nucleotide level at two to three orders of magnitude greater than normal cells [8]. The remaining majority of CRC cells bear the CIN phenotype, which is characterized by a greatly increased rate in the gain/loss of a whole chromosome or a large fraction of chromosomes, although the mechanisms underlying CIN remain largely unknown [9]. The alternation of the DNA index (DI) reflects an overall change in the chromosome. The DI, which was accessed by laser scanning cytometry (LSC), was suggested to be strongly associated with the

Dr. Oki and Dr. Zhao designed the project, planned the experiments and designed the methods; Dr. Ando was involved in the analyses and experiments; Dr. Morita, Dr. Kakeji and Prof. Maehara contributed to the presentation, interpretation and discussion of the results obtained in article form.

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chromosomal aberrations detected by fluorescent in situ hybridization [10].

The *p53* pathway is responsible for a variety of intrinsic and extrinsic stress signals that impact cellular homeostatic mechanisms that monitor DNA replication, chromosome segregation, and cell division alternations [11]. A *TP53* gene defect is one of the most common genetic alternations in CRC as well as many malignancies [12]. Classically, a mutation and a loss of heterozygosity (LOH), i.e., the "two hits," of *TP53* finally lead to the occurrence of a defect in the p53-related pathways [13].

One interesting study suggests that the inclusion of MSI tumors account for the location-related difference of colon cancer [14]. The study estimated the p53 defects by immunohistochemical staining. This concept was herein examined by standard methodologies in a series of Japanese patients. Rectal cancer was also included in the study panel.

2. Materials and methods

2.1. Patient selection and sample preparation

This study enrolled 180 Japanese patients diagnosed to have CRC who underwent surgery without neoadjuvant chemotherapy in the Department of Surgery II at Kyushu University Hospital from 1994 to 2003. Written informed consent for the study of excised tissue was obtained from each patient. The entities of the proximal colon (cecum, ascending colon, and transverse colon), distal colon (descending and sigmoid colon), and rectum were defined by separation of the splenic flexure and height of the promontorium.

DNA was extracted from cancerous tissue specimens and the corresponding noncancerous mucosa specimens [15]. The remaining specimens were routinely processed for the histopathologic analysis and diagnosis.

2.2. Microsatellite analysis for MSI and LOH detection

High-resolution fluorescent microsatellite analysis has been described in detail elsewhere [15]. Briefly, genomic DNA isolated from cancerous and corresponding noncancerous tissue specimens was used to amplify microsatellite loci by polymerase chain reaction (PCR) using primer sets labeled with a fluorescent compound, ROX (6-carboxy-x-rhodamine) or HEX (6-carboxy -20,40,70,4,7, -hexachloro-fluorescein). The fluorescently labeled PCR products were mixed, denatured, and loaded onto an ABI 310 sequencer (Applied Biosystems, Foster City, CA) for fragment analysis. The data were processed using the GeneScan software package (Applied Biosystems).

An alteration in the length of a microsatellite PCR fragment from cancerous tissues was MSI positive. MSI is defined by the frequency of positive findings of five reference markers [16]. MSI status is classified as follows: microsatellite instability high (MSI-H), more than 30% of loci demonstrate MSI; microsatellite instability low, 30% or less loci demonstrates MSI; and microsatellite stability, no MSI detected. MSI-H is labeled "MSI (+)" and the rest "MSI (−)"[16].

D17S796 and D17S1353 were used as markers for *TP53* gene LOH detection. LOH was defined as the presence of heterozygous peak heights in more than 30% of alleles in either of the loci tested [17]. If the two clusters overlapped in their electrophoresis profile, the case was not informative (NI) regarding LOH estimation.

2.3. Determination of the DNA Index (DI)

LSC (CompuCyte Corporation, Westwood, MA) was used to detect the chromosomal DNA content; i.e., DI as described [18]. In brief, cell nuclei were recovered from two pieces of a 50 μm-thick slice from paraffin-embedded blocks that had a tumor area greater than 30% in dimension. Single-layered nuclei were spread on a slide glass, stained with propidium iodide/RNase A (Sigma, St. Louis, MO), covered, and observed. A DNA content histogram was generated, and DI was calculated according to previously published guidelines [19]. The DI of lymph cell nuclei with dimensions of about 40 μm^2 was used as the reference (DI = 1.0). Tumors with a single peak of DI < 1.2 were defined as diploid or, otherwise, as aneuploid [20].

2.4. TP53 gene mutational analysis

TP53 exons 5–9, including exon–intron junctions, were amplified by PCR using "p53 primers" (Nippon Gene,

Table 1
Clinicopathological backgrounds of proximal and distal colon cancer

	Location		
	Proximal	Distal	*P*
Age (mean)	66.2	62.7	0.119
Gender			
Male	33	28	0.900
Female	26	21	
Gross			
Polypoid	49	43	0.493
Flat	10	6	
Histologic grade			
Grade 1	28	28	0.293
Grade 2	18	18	
Grade 3	13	3	
pStage			
I–II	29	21	0.514
III–IV	30	28	
Lymphocyte infiltration[a]			
Negative	31	24	0.736
Positive	26	23	
Lymphatic invasion[b]	2	2	
None	33	33	0.185
Present	25	15	

[a] Four missing data.
[b] Two missing data.