Table 4 Description of non-surgical treatment of nonresection group and group A

	Nonresection group	Group A	p-value
No. of patients	19	22	
Age at recurrence *	59.8 (43-74)	54.5 (35-78)	0.08
Sex ratio			
Male/Female	11/8	15/7	0.53
Non-surgical treatment after local recurrence			
Radiation therapy			
Yes/No	15/4	19 **/3	0.68
Intra-venous chemotherapy			
Yes/No	8/11	12/10	0.54
Intra-arterial chemotherapy			
Yes/No	3/16	1/21	0.32
Oral chemotherapy			
Yes/No	9/10	12/10	0.76

* values are mean (range). ** includes pre-, intra- and post-operative radiotherapy.

Fig. 9 Survival after diagnosis of local recurrence in patients of nonresection group and group A.

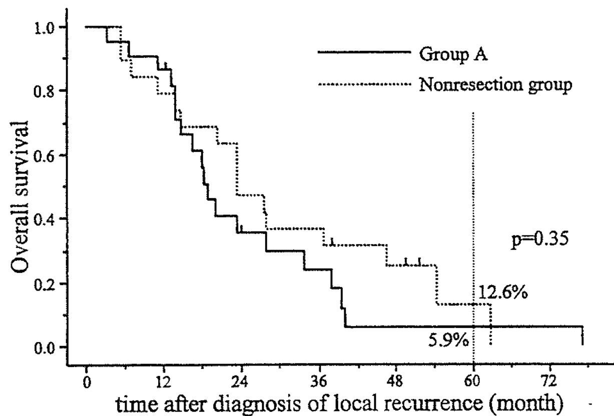
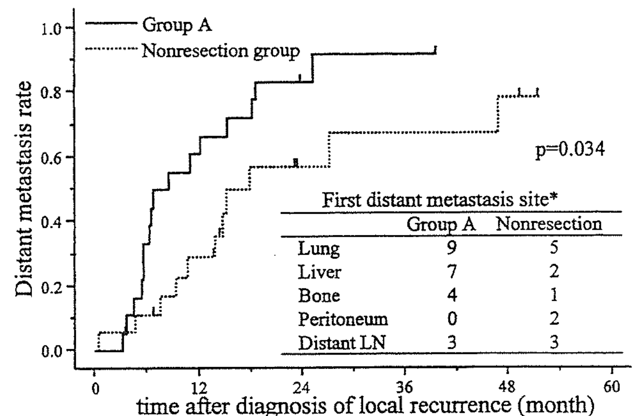


Fig. 10 Distant metastasis after diagnosis of local recurrence in patients of nonresection group and group A. *:Data are overlapping;some distant metastases were detected at the same time. LN: lymph nodes



はない.

切除術式別の遠隔成績について，赤須ら[17]は直腸切断術群や再発巣切除術群に比べ括約筋温存術群が予後良好であったと報告している．加藤ら[16]は骨盤内臓器全摘術がその他の術式より予後良好であったと報告している．今回，術式別に遠隔成績を検討したところ，骨盤内臓器全摘術群に予後良好な傾向はあるものの有意な差は認められなかった．

再発腫瘍が存在する部位や，再発様式別に遠隔成績を評価したという報告も散見される．Hahnloser ら[23]は術前や術中の所見において腫瘍の骨盤壁への固定箇所が多いほど予後が不良であると報告し，Yamada ら[30]は骨盤の側壁や高位仙骨に浸潤のあるものは予後が悪いと報告している．また赤須ら[17]は，局所再発形式別では吻合部再発で最も生存率が良く，骨盤壁再発が最も不良であったと報告している．これらの報告から，骨盤壁に浸潤があるような場合は手術成績が悪いことが予想される．しかし，いずれも術中所見や術後病理所見からの検討で，術前診断から治療方針を検討した研究はない．

そこで今回，術前画像診断の所見から，腫瘍進展部位を3群に分類した．腫瘍が接しているだけか浸潤しているかの評価は，診断医の主観が入りやすく客観性に欠けるため，接しているものはす

べて浸潤しているものと同様に扱った.

A群では有意に治癒切除率が低く，予後も不良であった．またB, C群ではR0群の局所再々発率は低く，予後も良好だが，A群ではR0群，R1群にかかわらず，ほぼ全例で術後2年以内に局所再々発が出現し，術後3年以内に死亡した．術前画像診断で再発腫瘍が骨盤壁に接する場合，術前診断が過小評価の傾向にあり，術前に切除可能と診断しても治癒切除できる症例は少ない．また，仮に治癒切除できたとしても，ほぼ全例で局所に腫瘍細胞が残存する可能性が高い.

再切除術後の遠隔転移については，B, C群では共に半数以下であるのに対し，A群で有意に多く，半数以上の症例が7か月以内に出現した．また，A群と非切除群を比較すると，生存率で有意差こそ認めなかったが，遠隔転移はA群で有意に早く発生していた．これらの結果から，A群では再切除術時にすでに遠隔転移が存在している可能性が高い．さらに，より進行していると考えられる非切除群より早期に遠隔転移が発生することから，遠隔臓器に潜在的に存在する微小転移病巣が手術侵襲による免疫力の低下などの理由でより早期に出現した可能性や，局所にとどまっていた腫瘍細胞が，手術操作により体循環に流入，遠隔転移を起こしたことなどが考えられる．いずれにせよ，再発腫瘍が骨盤壁に接する場合，腫瘍は局所に限局している可能性は低く，すでにsystemic diseaseになっている症例が多いものと考えなくてはならない.

今回の検討の結果から，術前画像診断で再発腫瘍が吻合部周囲に限局しているか，第3以下の仙骨や骨盤内臓に接するものは，外科的治療の成績が良く切除術の良い適応であると考える．しかし，再発腫瘍が第2以上の仙骨に接する，または梨状筋・内閉鎖筋などの筋性骨盤壁に浸潤または接する場合は，現在の治療法では十分な効果が得られているとは言い難い．このような症例には，手術適応や術式，補助療法の再検討が必要であり，さらに新たな治療法の検討も不可欠であろう.

局所治療については，術前の放射線化学治療が治癒切除率の向上に有効であるという報告もある[29][31]．また，最近では炭素イオン線などの重粒子線治療の報告もみられる．適応に制限があるものの高い局所制御率が報告されており[32]，今後注目される治療法である．また，術後早期の遠隔転移が多いことから，補助化学療法についても検討が必要であろう．術後化学療法は周術期の全身状態や術後合併症の影響で開始が遅れることがしばしばある．全身状態の良いときに行える術前補助化学療法は，高い確率で発生する術後遠隔転移に対し予防効果が期待しえると考える.

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The Effect of Surgical Treatment for Local Recurrence after Rectal Cancer Surgery : An Analysis based on the Preoperative Imaging Studies

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Background : Although surgical resection is the only therapeutic option for curing patients with local recurrence after rectal cancer surgery, the dismal prognosis often fails to justify the degree of adverse events associated with major surgery. To reassess the relevance of surgery, we analyzed the outcome of patients based on the site or extent of local recurrence classified based on preoperative imaging studies. **Patients and Methods** : Between 1981 and 2002, 84 patients with locally recurrent rectal cancer underwent curative surgery. They were classified into three groups based on the preoperative computed tomography or magnetic resonance imaging : recurrent tumors invading or touching the piriform muscles or internal obturator muscles, or touching the upper sacrum (S1, S2) (group A) ; recurrent tumors invading or touching the lower sacrum (S3, S4, S5) or the pelvic organs such as the prostate, the uterus, the seminal vesicles or the urinary bladder (group B) ; and recurrent tumors localized at the anastomosis site (group C). Prognostic data for 19 patients diagnosed during the same period who were found to have extensive tumoral invasion and were not indicated for surgery or failed to undergo resection were used for comparison (nonresection group). **Results** : Curative resection in all patients was 61.9%. That in group A was 31.8%, in group B 80.6%, and in group C 81.3%. Five-year survival following resection was 30.0% in all patients, 5.9% in group A, 32.7% in group B, and 67.0% in group C. The incidence of locoregional failure and distant metastasis following surgery for recurrent disease was significantly higher for Group A. The median interval between primary diagnosis of local recurrence and detection of distant metastasis was 8.4 months for group A and 18.0 months for the nonresection group, although no difference in overall survival was observed between the two groups. **Conclusions** : Patients in group A suffered from poor curative resection and early emergence of locoregional failure or distant metastasis, leading to a dismal prognosis. The indication for surgery, the optimal extent of surgical resection, and the application of adequate adjuvant therapies should therefore be seriously reconsidered for this subset of patients.

Key words : rectal cancer, surgery, local recurrence, site of local recurrence, preoperative imaging studies
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Extensive but Hemiallelic Methylation of the h*MLH1* Promoter Region in Early-Onset Sporadic Colon Cancers With Microsatellite Instability

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Background & Aims: Methylation of the h*MLH1* promoter region is frequently observed in microsatellite instability (MSI)–positive sporadic colorectal carcinomas. We studied h*MLH1* promoter methylation in peripheral blood lymphocytes of 87 index patients representing 29 cases of hereditary nonpolyposis colorectal cancers (HNPCCs), 28 cases of atypical HNPCCs, and 30 sporadic cases of the development of early-onset colorectal carcinomas or multiple primary cancers. Methods: Methylation of the h*MLH1* promoter region was analyzed by Na-bisulfite polymerase chain reaction/single-strand conformation polymorphism analysis or methylation-specific polymerase chain reaction. MSI, allelic status of the h*MLH1* locus, and loss of hMLH1 protein expression were examined in cases for which tumor tissues were available. Results: Extensive methylation of the h*MLH1* promoter was detected in peripheral blood lymphocytes of 4 of 30 patients with sporadic early-onset colon cancer, among whom multiple primary cancers (1 colon and 1 endometrial cancer) developed in 2 cases. This methylation was not detected in analyses of HNPCC or atypical HNPCC groups or healthy control subjects. MSI was positive, and extensive methylation was detected in both cancers (colon and endometrial cancer) and normal tissues (colon, gastric mucosa, endometrium, and bone marrow) in all of the examined cases (3 of 3). Analysis of a polymorphic site in the h*MLH1* promoter in 2 informative cases showed that methylation was hemiallelic. In 1 case, the unmethylated allele was lost in the colon cancer but not in the metachronous endometrial cancer. Conclusions: Constitutive, hemiallelic methylation of the h*MLH1* promoter region was shown to be associated with carcinogenesis in sporadic, early-onset MSI-positive colon cancers.

Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominantly inherited syndrome predisposing to cancers of the colorectum, endometrium, ovary, small intestine, and upper urinary tract.[1] The majority (85%–95%) of HNPCC tumors show microsatellite instability (MSI), which leads to the accumulation of deletion and insertion mutations at simple repeated sequences. In HNPCC, MSI is caused by germline mutations of mismatch repair genes (*MMR* genes) such as h*MSH2*, h*MLH1*, h*PMS1*, h*PMS2*, and h*MSH6*.[2–7] Among these *MMR* genes, mutations of h*MSH2* and h*MLH1* are known to be responsible for up to 45%–64% of HNPCCs.[8,9] HNPCCs are characterized phenotypically by early-onset colorectal carcinoma (CRC), prevalent tumor location in the proximal colon, and an increased risk of developing multiple CRCs and other malignancies.[10–13] On the other hand, some (10%–15%) sporadic CRCs also show MSI,[14–16] and methylation of the h*MLH1* promoter region has been suggested to be the major mechanism in these cases.[17–19] Methylation of the h*MLH1* promoter region and subsequent transcriptional silencing have been demonstrated in the formation of MSI-positive cancers.[17–21] In a previous study, methylation of the h*MLH1* promoter region induced transcriptional silencing of both of the h*MLH1* alleles in cell lines showing MSI[22] and this epigenetic mechanism of gene inactivation is in line with Knudson's two-hit hypothesis.[23] The proximal region of the h*MLH1* promoter contains cis-elements important for regulating gene expression.[24] Methylation of an adjacent CpG site inhibits binding of the core binding

Abbreviations used in this paper: BiPS, Na-bisulfite treatment and PCR single-strand conformation polymorphism; CRC, colorectal carcinoma; HNPCC, hereditary nonpolyposis colorectal cancer; LOH, loss of heterozygosity; *MMR* gene, mismatch repair gene; MSI, microsatellite instability; MSI-H, high-frequency MSI; MSP, methylation-specific PCR; PBL, peripheral blood lymphocyte; PCR, polymerase chain reaction; RT-PCR, reverse-transcription PCR; SSCP, single-strand conformation polymorphism.

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factor to the CCAAT box in this region and is one of the causes of h*MLH*1 gene silencing in colon cancer cells.[25] We reported that extensive methylation (designated as full methylation) of the h*MLH*1 promoter region played a crucial role in h*MLH*1 gene inactivation,[26] and that full methylation occurred in both alleles of the h*MLH*1 promoter region in high-frequency MSI (MSI-H) colon cancers.[27] In one third of the CRCs showing full methylation, methylation was also detected in the adjacent normal colonic mucosa, although it was confined to the most upstream region of the h*MLH*1 promoter sequences (designated as partial methylation).[27] Sporadic MSI-positive CRCs show different clinicopathological characteristics from those of HNPCC in that they are preferentially associated with late-onset proximal colon cancer in female patients,[26,28] suggesting that changes of hormonal status might be related to the development of the h*MLH*1 promoter methylation. Recently, Gazzoli et al.[29] examined 14 cases of suspected HNPCC with MSI-H but no detectable germline mutations of h*MSH*2, h*MLH*1, and h*MSH*6 for hypermethylation of the h*MLH*1 promoter region, and they reported a case in which 1 allele of h*MLH*1 was methylated in DNA isolated from blood, and biallelic inactivation of the h*MLH*1 gene in the tumor was caused by a loss of heterozygosity (LOH) of the other allele. They suggested that this was a novel mode of germline inactivation of a cancer susceptibility gene.

In this study we analyzed the methylation status of the h*MLH*1 promoter region in peripheral blood lymphocytes (PBLs) of patients referred to genetic counseling clinics because of the suspicion of an HNPCC. We detected constitutive methylation of the h*MLH*1 promoter region in 4 cases of early-onset sporadic MSI-H CRCs. They displayed hemiallelic but full methylation of the h*MLH*1 promoter region in normal tissues such as PBLs, normal colonic mucosa, endometrium, gastric mucosa, and bone marrow, exhibiting distinctly different clinical characteristics from both cases of HNPCC and cases of sporadic MSI-H CRC.

Materials and Methods

Patients

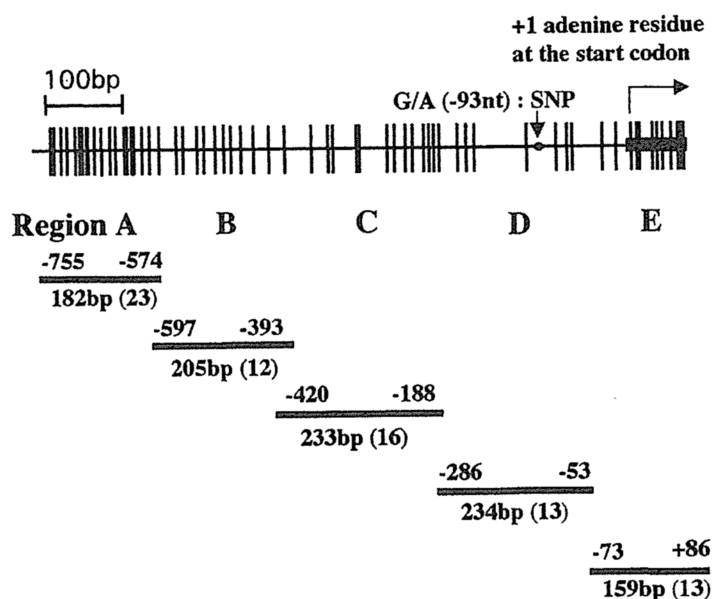
The study protocol was carried out after receiving institutional review board approval and written informed consent for the study from 87 index patients. PBLs were obtained from the 87 index patients, who visited genetic counseling clinics because of suspicion of HNPCC. All of these patients developed CRCs, and 29 of them fulfilled 1 of the 2 HNPCC criteria, i.e., the Amsterdam's minimum criteria or the modified Amsterdam criteria.[30–32] Twenty-eight kindred were classified as having atypical HNPCC, because they had at least 1 first-degree relative with CRC but did not fulfill the above-mentioned criteria. Of the kindred with atypical HNPCC, 13 kindred fulfilled the second (B-2) and/or fourth (B-4) criteria of the Bethesda guidelines,[33] i.e., individuals with 2 HNPCC-related cancers, including synchronous and metachronous CRCs or associated extracolonic cancers (5 cases) (B-2), individuals with CRC or endometrial cancer diagnosed at age younger than 45 years (6 cases) (B-4), and 2 cases fulfilled both of these 2 criteria (B-2 + B-4). Thirty kindred fulfilled neither the criteria for HNPCC nor atypical HNPCC. They developed early-onset CRCs when younger than the age of 50 years or multiple CRCs and/or extracolonic cancers, without showing familial predisposition to HNPCC-related tumors in their first-degree relatives. As to the relation with the Bethesda guidelines, the number of cases fulfilling the second or fourth criteria of the Bethesda guidelines was 4 (B-2), 20 (B-4), and 2 (B-2 + B-4), respectively. Regarding case H403, a case of sporadic CRC showing constitutive methylation of the h*MLH*1 promoter region, the proband's sister visited the clinic for genetic counseling, and her PBLs were examined for methylation. The methylation status of the h*MLH*1 promoter region was also examined in PBLs from 100 normal healthy control subjects older than 50 years undergoing routine health checkups. Before the analysis, samples were made unlinkable as to their personal information.

Analysis of MSI

In 4 cases showing aberrant methylation of the h*MLH*1 promoter region, the MSI status was examined in all available samples, including tumor tissues and normal tissues such as PBLs, colonic mucosa, gastric mucosa, endometrium, and bone marrow aspirate. Genomic DNAs were subjected to polymerase chain reaction (PCR) amplification at 9 microsatellite repeat loci (*D2S123*, *D5S346*, *D17S250*, *BAT26*, *BAT25*, *MSH3*, *MSH6*, *TGFBR2*, and *BAX*). Analysis of MSI was performed as described previously.[26] The definition of MSI status was as follows: high-frequency MSI (MSI-H), when 30% or greater of the 9 markers showed MSI, in accordance with the recommendation of the National Cancer Institute Workshop.[34]

Methylation Analysis of the h*MLH*1 Promoter Region

Na-bisulfite PCR/single-strand conformation polymorphism (SSCP) (BiPS) analysis was performed as described previously[26,35] (Figure 1). With the adenine residue at the start codon numbered as +1nt, the h*MLH*1 promoter (−755 to +86) was divided into 5 regions (region A [from −755 to −574, containing 23 CpG sites], B [from −597 to −393, 12 CpG sites], C [from −420 to −188, 16 CpG sites], D [from −286 to −53, 13 CpG sites], and E [from −73 to +86, 13 CpG sites]) and was amplified with 5 sets of PCR primers. Each primer set was designed to anneal to both methylated and unmethylated DNAs, of which the amplicons could be separated by SSCP analysis. Amplified DNA fragments were visualized by using SYBR Gold nucleic acid gel stain (Cosmo Bio



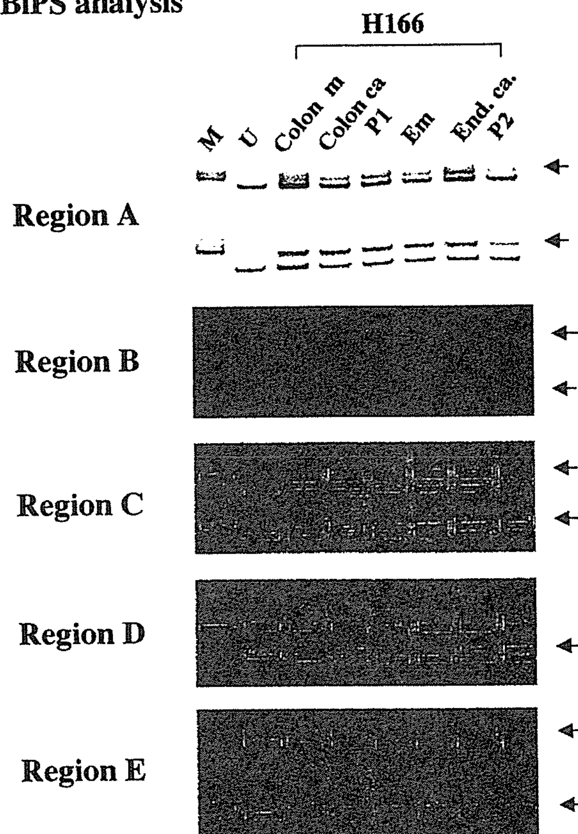


Figure 1. BiPS analysis of h*MLH1* promoter region and methylation profiles of various tissues in case H166. (*A*) Map of the 5′ CpG islands of the h*MLH1* gene. CpG sites are indicated by vertical lines. The arrow indicates G/A polymorphism at position −93nt in the h*MLH1* promoter region. The expected PCR products for regions A, B, C, D, and E are shown. Their positions relative to the adenine residue at the start codon and the sizes of the amplified DNA fragments are indicated. Figures in the parentheses indicate the numbers of CpG sites in each region. (*B*) Na-bisulfite treatment and PCR-SSCP (BiPS) analysis of the h*MLH1* promoter region in each tissue of case H166 (M, control methylated DNA; U, control unmethylated DNA; Colon m, colon normal mucosa; Colon ca, colon cancer; P1, PBLs obtained at 34 years of age (diagnosed with colon cancer); Em, endometrium; Eca, endometrial cancer; P2, PBLs obtained at 44 years of age (diagnosed with endometrial cancer). We divided the h*MLH1* promoter into 5 regions (regions A–E) and examined the methylation status. DNAs from all samples in case H166 showed methylated bands in all regions, indicating full methylation of the h*MLH1* promoter region, which was confirmed by direct sequencing of the mutated bands (data not shown).

Co., Tokyo, Japan) and scanned with a Fluorescent Image Analyzer Model FLA-3000G (Fuji Photo Film Co., Tokyo, Japan). When the bands showed mobility shifts, they were cut from the gel, reamplified, and directly sequenced without subcloning by using an ABI 310 PRISM sequencer (Perkin-Elmer Co., Branchburg, NJ) with a Big-Dye Terminator Cycle Sequencing Ready Reaction Kit (PE Applied Biosystems, Foster City, CA). Full methylation was defined as the state in which all CpG sites from regions A through E were methylated.[26,27] The allelic status of methylation was examined by direct sequencing of the G/A polymorphic site at −93nt in region D.[36] Furthermore, the methylation status of the h*MLH1* promoter region D was also analyzed by methylation-specific PCR (MSP) as described previously[27] (Figure 2*B* and *C*). The PCR product was mixed with 5× loading buffer, electrophoresed on a nondenaturing 8% polyacrylamide gel, stained with ethidium bromide, and scanned with a Fluorescent Image Analyzer Model FLA-3000G. DNA fragments amplified by MSP were subjected to direct sequencing, and G/A polymorphism was examined to determine whether the methylation was a biallelic or hemiallelic event.

Mutation Analysis of the h*MSH2* and h*MLH1* Genes

Total RNA was extracted from the PBLs treated with puromycin by using the acid guanidine phenol chloroform method.[37] Long reverse-transcription (RT)–PCR was carried out from RNAs extracted from PBLs incubated in the presence of puromycin, according to the method we reported previously.[38,39] Signals from mutated alleles are enhanced after puromycin treatment as a result of the suppression of nonsense-mediated mRNA decay and easily distinguishable from signals from the wild-type allele. This approach is a sensitive method to screen deleterious mutations such as nonsense or frameshift mutations and large genomic disorganizations resulting in genomic deletion or partial duplication of the h*MLH1* gene.[39] Sequencing reactions were performed by using a Big-Dye Terminator Cycle Sequencing Reaction kit. Elec-

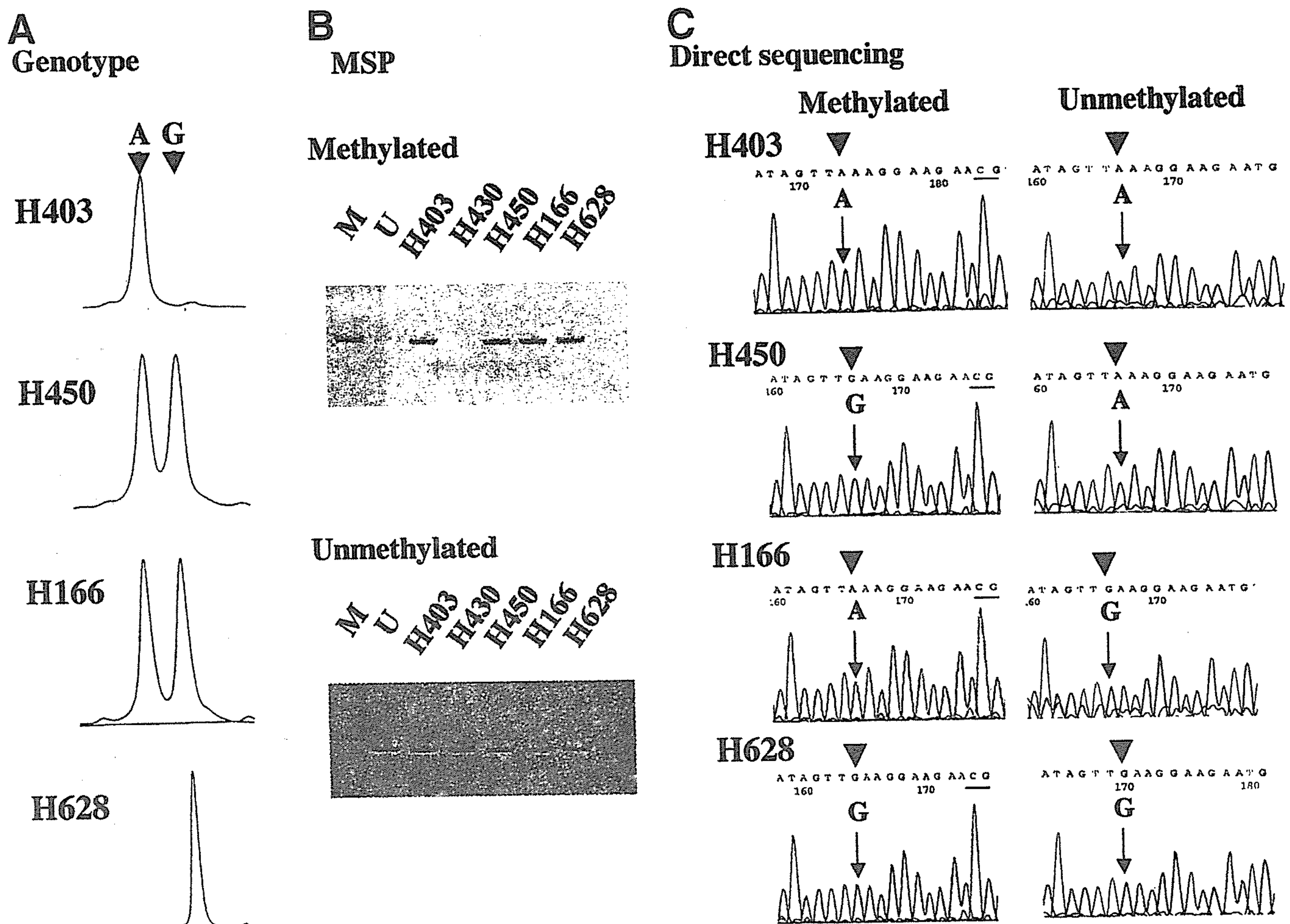


Figure 2. Uniparental methylation of the h*MLH1* promoter region. (*A*) PCR/SSCP analysis of the SNP at position −93nt was used to determine the genotype of 4 cases, i.e., A/A for H403, A/G for H450 and H166, and G/G for H628. (*B*) MSP analysis of the h*MLH1* promoter region D. M, control methylated DNA; U, control unmethylated normal DNA. DNA derived from H403, H450, H166, and H628 showed a methylated band in the promoter region D. DNA derived from H430 (unaffected sister of H403) did not show a methylated band. In addition, DNA derived from all cases showed an unmethylated band in the same region. (*C*) Direct sequencing of the PCR products derived from the methylated and unmethylated fragments in MSP analysis. The arrow indicates G/A polymorphism at position −93nt in the h*MLH1* promoter region. One allele (allele G in H450, allele A in H166) was observed to be a methylated fragment, and the other allele (allele A in H450, allele G in H166) was observed to be an unmethylated fragment.

trophoresis was carried out by using an ABI 310 PRISM sequencer. Primers used for direct sequencing were described in a previous report.[38] All mutations detected by direct sequencing were confirmed by PCR-based sequencing of the corresponding region of genomic DNA.

Analysis of Allelic Loss of h*MLH1*

Analysis of LOH of h*MLH1* was performed as described previously[27,40] (Figure 3). Briefly, an ALFexpress DNA sequencer (Pharmacia, Tokyo, Japan) was used for SSCP analysis. Electrophoresis was performed at 20W for 1500 minutes with a 15% polyacrylamide gel. During electrophoresis, the gel was kept at a constant temperature of 16°C by using a circulating water bath. The data were analyzed by using the software package Fragment Manager (Pharmacia, Tokyo, Japan). LOH was defined when the peak height of the signal from either allele was decreased more than 50% as compared with that of the normal control.

Immunohistochemical Examination of h*MLH1*

Immunohistochemistry was performed as described previously[26] (Figure 4). Briefly, tissue sections were deparaffinized with xylene and dehydrated by using a graded series of ethanol. Antigen retrieval was performed in citrate buffer by using a heat-induced microwave oven. The avidin-biotin–conjugated immunoperoxidase technique was performed by using a DAKO LSAB2 Kit (DAKO, Carpinteria, CA). Endogenous peroxidase activity was blocked by methanol supplemented with 0.02% H_2O_2. Sections were immersed in 4% commercial nonfat skim milk powder to inhibit nonspecific antibody binding. The sections were then incubated overnight

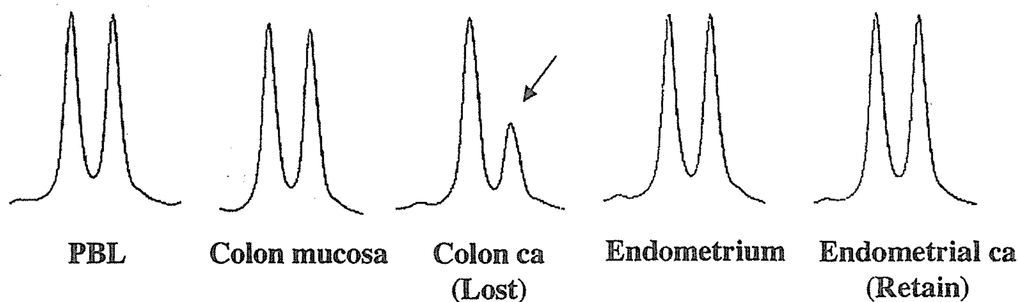


Figure 3. Electropherograms of SSCP analysis showing allelic loss of h*MLH1* in colon and endometrial tissues of case H166. Allelic loss was detected only in the colon cancer, and the position of the lost allele is indicated by an *arrow.*

with mouse monoclonal antibody to the h*MLH*1 gene product (clone G168-15; PharMingen, San Diego, CA) (at a 1:50 dilution) and then with biotinylated secondary antibody and peroxidase-labeled avidin-biotin complex for 30 minutes, and staining was visualized by incubating the sections with 0.02% H_2O_2 and 0.02% diaminobenzidine in methanol for 10 minutes.

Results

Characteristics of Four Cases With Extensive Methylation of h*MLH1* Promoter Region in PBLs

Analysis of PBLs from 87 index patients in whom HNPCC was suspected revealed extensive methylation of the h*MLH*1 promoter region in 4 cases (H166, H403, H450, and H628), whose characteristics are shown in Table 1. They were characterized by early-onset colon cancer and absence of family history of CRC in their first-degree relatives. Case H166 developed ascending colon cancer and endometrial cancer at the ages of 38 and 44 years, respectively, and PBL samples taken after the onset of each cancer showed extensive methylation of the h*MLH*1 promoter region. Case H628 developed descending colon cancer at 29 years of age and had a history of left colectomy as a result of descending colon cancer at 17 years of age.

We examined MSI and methylation status of the h*MLH*1 promoter region in colon cancer (H403, H166, and H628), endometrial cancer (H166) tissues, and in their normal counterparts (Figure 1*B*, Table 1). All of the

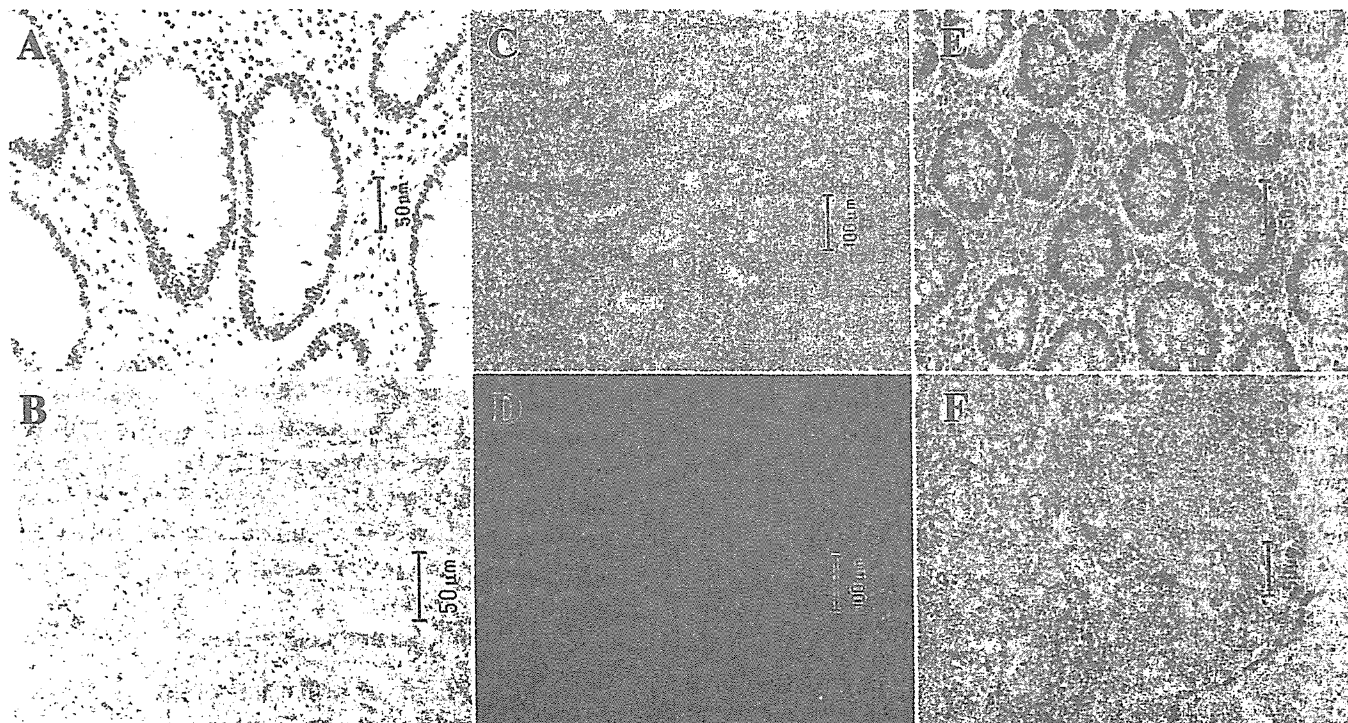


Figure 4. Immunohistochemical staining for h*MLH1* expression in colon tissues of case H166 (*A, B*) and H628 (*E, F*) and endometrial tissues of case H166 (*C, D*). Positive nuclear staining was observed in normal colonic mucosa (*A, E*) and endometrium (*C*), whereas a lack of positive nuclear staining was observed in carcinomas of the colon (*B, F*) and endometrium (*D*).

Table 1. Characteristics of Patients With Extensive Methylation of h*MLH1* Promoter Region in Lymphocyte Cells

				Family history						h*MLH1*			
Case	Age[a]	Sex	Site	CRC[b]	Other cancer	Genotype[c]	Specimen		MSI	Methylation	Mutation[d]	IHC	h*MSH2* mutation
H166	38	F	A	–	—	A/G	PBL	38 yr	MSS	Full	–		–
							Colon mucosa		MSS	Full		+	
							Colon cancer		MSI-H	Full		–	
							PBL	44 yr	MSS	Full	–		–
							Endometrium		MSS	Full		+	
							Endometrial		MSI-H	Full		–	
							cancer		MSS	Full			
							Colon mucosa	45 yr	MSS	Full			
								(biopsy)					
							Gastric mucosa		MSS	Full			
							Bone marrow						
H403	28	M	T	–	Gastric cancer	A/A			MSS	Full	–		–
					(grandfather)								
							PBL		MSS	Full		N.D.	
							Colon mucosa		MSI-H	Full		N.D.	
							Colon cancer						
H450	23	F	A	–	Pancreas cancer	A/G	PBL		MSS	Full	–		–
					(grandmother)								
H628	29	M	D (17 yr)	–	Gastric cancer	G/G			MSS	Full	–		–
					(grandfather)								
			A (29 yr)				PBL		MSS	N.D.		+	
					Breast cancer (aunt)		Colon mucosa		MSI-H	N.D.		–	
							Colon cancer	(biopsy)	MSS	Full			
					Breast cancer (aunt)		Colon mucosa	(biopsy)	MSS	Full			
							Gastric mucosa						

IHC, immunohistochemical analysis; A, ascending colon; MSS, MSI-stable; T, transverse colon; N.D., not done; D, descending colon; PBL, peripheral blood lymphocyte; MSI-H, high-frequency MSI; +, positive staining; –, negative staining.
[a]CRC onset age.
[b]No family history of CRC.
[c]h*MLH1* promoter genotype (−93 nt from translation start site).
[d]Mutation negative.

tumors showed MSI-H, and extensive methylation of the h*MLH*1 promoter region was demonstrated in both tumors and normal mucosa. In cases H166 and H628, the patients underwent further examinations postoperatively such as digestive endoscopy (H166 and H628) and bone marrow aspiration (H166) for persistent leukopenia.

In both cases, methylation of the h*MLH*1 promoter region was shown to be constitutive and hemiallelic in all samples examined. PBLs of case H403's sister (H430) did not show the methylation (Figure 2*B*). The PBLs of the other family members were not available. No germline mutations were detected in the h*MLH*1 or h*MSH2* genes of these 4 patients. Methylation of the h*MLH*1 promoter region was not detected in the PBLs of 100 healthy blood donors.

Hemiallelic Methylation of h*MLH1* Promoter Region in Normal Tissues

We previously reported that methylation of the h*MLH*1 promoter region was a biallelic event in MSI-positive CRCs.[27] To determine whether methylation of the h*MLH*1 promoter region in PBL is a biallelic epigenetic event, we examined the methylation status of this region by using G/A polymorphism at position −93nt in the h*MLH*1 promoter by use of MSP combined with DNA sequencing (Figures 1 and 2*A*). In the 2 informative cases, we could confirm that methylation was hemiallelic (allele G in H450, allele A in H166) in all specimens.

Immunohistochemical Assessment of hMLH1 Protein Expression

To determine whether h*MLH*1 gene inactivation was caused by extensive methylation of the h*MLH*1 promoter region, we investigated hMLH1 protein expression in colon (cases H166 and H628) and endometrial (case H166) tissues by immunohistochemistry (Figure 4). hMLH1 protein expression was not detected in colon or endometrial cancer, but it was detected in normal colonic mucosa and endometrium.

Cause of Lack of hMLH1 Protein Expression in Cancer Tissues

To determine how the hemiallelic methylation of the h*MLH*1 promoter region induced silencing of

hMLH1 protein expression in cancer tissues, we investigated the LOH of h*MLH*1 in case H166 (Figure 3). Analysis of the colon cancer showed somatic loss of the G allele at the h*MLH*1 locus, and biallelic inactivation of the h*MLH*1 gene was caused by extensive methylation of allele A, followed by loss of the opposite allele. However, analysis of the endometrial cancer did not show LOH, and thus we could not identify the cause of the reduced expression of hMLH1 protein in endometrial cancer.

Discussion

In the present study we examined the methylation status of the h*MLH*1 promoter region in 87 index patients in whom HNPCC was suspected. The 87 index cases included 30 cases that were sporadic but had developed early-onset CRCs or multiple primary cancers. We identified 4 of 30 sporadic cases with extensive methylation of the h*MLH*1 promoter region in PBLs. They all developed CRCs at a very young age (the age at onset for a first cancer varied from 17 through 38 years of age), and there were no HNPCC-related cancers in their first-degree relatives. Analysis of 2 cases heterozygous for a G/A polymorphism at position −93nt showed that the methylation was hemiallelic (Figure 2*C*). These findings were in accord with those of a case reported by Gazzoli et al.[29] Those authors reported hypermethylation of the h*MLH*1 promoter region in 1 allele in the DNA from PBLs of a CRC patient with young age (25 years) at onset and without family history of CRC. We examined the methylation status of the h*MLH*1 promoter region in DNAs from various tissues, including normal mucosa of the colon, stomach, and endometrium and bone marrow, and the methylation was invariably detected in all tissues examined. Methylation occurred as a constitutive, hemiallelic event. All of these 4 cases were early-onset, and they were also sporadic without family history of HNPCC-related tumors in their first-degree relatives. PBLs of case H403's sister (H430) did not show the methylation (Figure 2*B*). The PBLs of the other family members were not available. Constitutive methylation of the h*MLH*1 promoter region was not detected in analyses of HNPCC or atypical HNPCC groups or healthy control subjects. Taken together, these findings suggest that hemiallelic methylation was not heritable, and that it was inconsistent with the mode of autosomal dominant mendelian inheritance, although aberrant methylation might be due to other unknown genetic mechanisms.

In MSI-H CRCs, methylation of the h*MLH*1 promoter region has been reported to be extensive, usually occurring in both alleles of the h*MLH*1 promoter, and strong association has been observed between the methylation profile of the h*MLH*1 promoter region and the clinicopathologic background of the cases, i.e., preferential occurrence in the proximal colon, female predominance, and older age at onset.[26,28] The 4 cases studied here showed different characteristics from ordinary MSI-H tumors in that the methylation was a constitutive but hemiallelic event, preferentially observed in early-onset CRC and without gender specificity (2 male and 2 female patients). The frequency of constitutive methylation of the h*MLH*1 promoter region was 13.3% (4 of 30 cases) in the cases of sporadic CRCs we examined, suggesting that hemiallelic methylation of the h*MLH*1 promoter region accounts for a subset of early-onset sporadic CRCs with MSI-H. Liu et al.[41] identified 1 case of germline mutation in early-onset CRC showing MSI, but the previously reported rates of detection of mutations in the *MMR* genes in early-onset CRCs were low.[42–44] A study of 31 patients younger than 35 years of age and not fulfilling the Amsterdam minimum criteria, in which MSI was exhibited in 18 cases (58%), was also reported.[45] Twelve of those cases were evaluated for alterations of *MMR* genes, and 5 (42%) were found to harbor germline mutations of either h*MSH*2 or h*MLH*1. Germline mutations of *MMR* genes might account for a part of early-onset CRCs, and some of them are suspected to be de novo mutations.

In our analysis of 30 sporadic cases, we detected 3 cases of germline mutations of the *MMR* genes (data not shown), whereas no germline mutations of h*MSH*2 or h*MLH*1 were detected in analyses of the 4 patients described here. Genomic disorganizations such as large deletions or duplications of the *MMR* genes have been thought to occur in a considerable proportion of HNPCC cases.[46,47] Previously, we reported 2 cases of genomic deletion and 1 case of partial duplication of the h*MLH*1 gene that were detected by using long RT-PCR from puromycin-treated samples, and this method is sensitive enough to screen large genomic disorganizations of the *MMR* genes.[39] Recently, several genes were reported to be involved in familial predisposition to CRC.[48–50] In the case of h*MSH*6, many of the mutation carriers develop carcinomas of the distal colon and endometrium, and analysis of tumor tissues showed that half of them were MSI-negative.[48] As for MYH, the mutation carriers showed autosomal recessive inheritance, whereas their phenotypes were characterized by the presence of multiple colorectal adenomas.[49,50] The clinical characteristics of our cases seem to be incompatible with mutations of these 2 genes.

In case H166, biallelic inactivation of the h*MLH*1 gene in colon cancer was caused by an LOH of the

unmethylated allele (Figure 3). Gazzoli et al.[29] reported that biallelic inactivation resulted in loss of hMLH1 protein expression in the tumor and suggested a novel mode of germline inactivation of a cancer susceptibility gene. These results were inconsistent with our previous study showing that allelic loss of the h*MLH*1 locus was infrequent, and methylation was biallelic in the majority of the ordinary MSI-H sporadic CRCs.[27] All of the 4 cases examined here were postoperative, and it remains unclear when the methylation of the h*MLH* gene occurred.

In case H166, the patient developed ascending colon cancer at the age of 38 years and endometrial cancer at the age of 44 years. In case H628, the patient developed descending colon cancer at the age of 17 years and ascending colon cancer at the age of 29 years (Table 1). In retrospective analysis, MSI-positive sporadic CRC patients have been reported to be at risk for developing extracolonic cancers and metachronous multiple CRCs.[51–54] Full methylation of the h*MLH*1 promoter region in PBLs might have a significant influence on the carcinogenesis of these multiple primary cancers and might be a potent diagnostic marker for identifying individuals at high risk of developing cancer.

In conclusion, we have tentatively identified a rare group of patients who have the MSI-H phenotype, show early-onset colon cancers without a family history of CRC, and exhibit extensive but hemiallelic methylation of the h*MLH*1 promoter region in PBLs and other normal tissues.

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［連載］

最新 癌の化学療法マニュアル

第①回 総論

島田安博*

はじめに―抗癌薬治療の意義

消化器癌をはじめとする固形癌に対する抗癌薬治療は，癌患者の多くをその治療対象とするが，有効な抗癌薬がなく，しばしば臨床的意義が疑問視されていた．すなわち，消化器毒性，血液毒性，神経毒性などの有害事象（副作用）と臨床効果とのバランスが妥当であるかという点である．手術不能癌に対する治療法として，抗癌薬治療の選択肢しか考慮されなかった時代には，患者の全身状態が不良であってもわずかの可能性に期待して抗癌薬治療を実施することもあった．最近では，ランダム化比較試験（RCT）により，抗癌薬治療を用いない群と積極的に抗癌薬治療を用いる群の治療成績を生存期間で比較・検討した結果が報告されている．胃癌や大腸癌では生存期間が2～3倍に延長することが示され，全身状態の良好な患者に対して積極的に抗癌薬治療が実施されている．これらのデータは抗癌薬治療が可能であった群と不可能であった群の比較でないことが重要である．不可能である群は，予後不良な患者が多く含まれ治療効果を見かけ上わるくみせるからである．

Ⅰ 抗癌薬治療の適応とインフォームド・コンセント

抗癌薬治療の適応については，一般に以下の適応規準が用いられている．一般診療においては，これらを遵守することができない状況も起りうるが，そのさいには患者自身に十分に治療の必要性を説明する必要がある．

1）組織学的に癌の診断がされている．

2）転移を有し，治癒切除が不能である．術後補助療法の場合には，治癒切除が実施されたが，術後再発のリスクが高いと判断される症例．術前投与の場合には，抗癌薬投与後に治癒切除が期待される症例．

3）全身状態の指標であるPS（performance status）が0～1である．PS 2以上については有害事象が高度になる可能性も高く，適応を慎重に判断する．PS 4は一般に適応はない．

4）年齢：20～75歳を目安とする．全身状態が良好であれば高齢者への抗癌薬治療は必ずしも禁忌ではないが，臓器機能が潜在的に低下している可能性があり，慎重な適応判断が必要である．

5）主要臓器機能が保たれている．WBC，PLTなどの血液検査，T-Bil，AST/ALT，血清CREなどで規準を規定する．

6）術前・術後の抗癌薬治療については，対象とする病期，根治度，治療開始と手術との間隔の規定などが必要である．術後補助療法では，手術の影響から回復を待って4～8週を目処に抗癌薬治療を開始することが多い．

7）患者本人からインフォームド・コンセントが得られている．治療に関する説明と同意に関しては多くの議論が行われてきたが，現在では十分

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な説明の後，本人より文書にて同意を得ることが標準的である．癌の診断名，病期，治療内容，有害事象，合併症，治療関連死亡，医療費，他の治療法の選択肢などについて事前に説明し，患者自身から治療に関する同意を得ることが必須である．とくに試験的治療では，施設倫理審査委員会(IRB)の承認済みの書類にて実施することが義務づけられている．多忙な臨床現場で，このような時間を要する説明を行うことはたいへんであるが，治療を患者と医療者の共同作業と理解すれば，重要であることは明らかである．

8) 治療の妨げとなる合併症は除外するか，適切に治療を行いコントロールすることが必要である．高血圧，糖尿病，心臓病など，患者の高齢化に伴い生活習慣病を合併する患者は多くなっている．

Ⅱ 標準治療の確立とRCT―治療ガイドラインの意義

最近では多くの癌腫に対して治療ガイドラインが作成され発表されている．医師向けあるいは患者・家族向けが公表され，情報公開，情報共有にきわめて重要な役割を担っている．ガイドラインは本来RCTによる臨床試験成績に基づき，作成委員会でエビデンスが選別され，素案が作成される．その後，作成とは関連のない評価委員会にて科学的臨床的な妥当性が外部評価され，公表される．新規エビデンスが発表されると再度吟味されて改訂される．抗癌薬治療に関しては海外での多くのRCTによるエビデンスに基づき，エビデンスレベルと推奨度が決定されて公表されている．しかしながら，診断法や手術方法などに関しては，歴史的にRCTになじまず，手技の工夫，発明により進歩し，安全性，有効性が確認され臨床に受け入れられている．したがって，欧米式のガイドラインには厳密には当てはまらないが，国内を中心に多くの臨床実績が積まれており，これらを基礎に一般臨床を実施することは妥当であると考える．臨床実績が学会などの全国規模の組織で管理，維持されて一定の質が保証されており，膨大な症例数を経験しているがんセンターなどの専門病院の臨床成績に基づくのであれば，受け入れは可能と考える．当然，将来的にRCTを計画実施して新規エビデンスの創生が必要であることはいうまでもない．

「標準治療」という言葉がガイドラインではしばしば使用されている．これの対語としては「試験治療」がある．胃癌治療ガイドラインでは，混乱した臨床現場を整理する目的もあり，治療法を「日常診療におけるStage分類別の治療法の適応」と「臨床研究としてのStage分類別の治療法の適応」に二分し，これになじみ深いT分類，N分類に基づくStage分類を重ねて整理している．「日常診療」ではここまでは実施しても過去の臨床実績からは治療成績は保証できる(確立された治療法)と明示している．一方，「臨床研究」に含まれる治療法は，現在検討中であり，確立された治療法ではないことを示している．もちろん，経験のある施設では「臨床研究」の治療法が「日常診療」になっていることもありうる．しかしながら，個々の治療法が現時点で確立された「日常診療」であるか，未確定要素を含んだ「臨床研究」であるかを治療担当医に認識をしてほしいということがガイドライン作成委員会の強い意向である．

臨床実績から臨床試験へ，データからエビデンスへ，今外科医が大きく変貌しつつあると内科医からもしっかり認識される．胃癌における大動脈周囲リンパ節郭清意義を検証するRCT，噴門部胃癌に対する開胸アプローチを検証するRCT，胃癌脾摘の意義を検証するRCT，胃癌腹腔鏡手術の意義を検証するRCT，直腸癌側方リンパ節郭清の意義を検証するRCT，結腸癌腹腔鏡手術の意義を検証するRCTなど手術手技を検証する多くのRCTが国内で実施されている．数年後には国内発のRCTエビデンスによるガイドラインの改訂が現実のものになることは確実である．このような臨床試験指向の中で，再度抗癌薬治療に関するRCTも見直されている．多くの術後補助療法や化学放射線療法のRCTがきわめて質の高い試験として実施されている．臨床医が臨床試験の意義に目覚めたともいえる大きな意識変化である．国内での臨床実績をRCTという国際共通語

で翻訳し，海外に向けて積極的に情報発信を目指しているのである．

治療ガイドラインを通じて日本全国の治療担当医が共通の認識で治療を行うことにより，治療格差が最小となることが理想である．さらに，ガイドラインに採用されている治療レジメンの根拠やその実際に関しても多くの雑誌で取り上げられているので参考にしていただきたい．また，各学会のホームページや日本病院機能評価機構のMINDSのウェブサイトでも概要や主要文献の抄録が確認できる．

Ⅲ 補助療法と転移性癌に対する抗癌薬治療

抗癌薬治療は，大きく分けて主たる治療法である手術療法と関連して実施される術前・術後補助療法と，切除不能進行・再発の転移性癌に対する抗癌薬治療の二つがある．

治療の目的は，前者は治癒切除の効果をより増強し治癒を目指す目的であり，後者は腫瘍増大による症状コントロールが目的である．したがって，治療方針に関しても若干異なる．補助療法では，転移性癌で有用性の確認された治療レジメンを最大限の支持療法を行って治療強度を維持して実施する．一方，転移性癌に対する治療も同様ではあるが，減量や休薬を適宜行い，腫瘍増大を抑制する期間を延長することがポイントとなる．このコンセプトは，従来行われてきた補助療法は少量長期間経口抗癌薬投与というものとまったく異なる．最近では，術後補助療法が転移性癌を対象としたRCTで評価された治療レジメンを減量なしにそのまま適応して再発抑制を確認していることが多く，結果的にもこの戦略により，術後補助療法の標準治療が確立されてきている．Stage Ⅲ結腸癌に対する5-FU/leucovorin(LV)，FOLFOX，胃癌に対するS-1などはこの開発戦略による成果である．術後の回復状態が不十分であるので，減量して実施する，あるいは再発までの長期間継続することについての十分なエビデンスはないと考えられ，現状では臨床試験で規定された治療期間を基本として一般臨床では実施すべきと考えられる．

Ⅳ 経口抗癌薬の臨床的意義―日本における問題点

消化器癌や乳癌では，従来から治療担当医が外科医であることが通常であった．これは国内の癌治療が診断は内科，外科治療・抗癌薬は外科というすみ分けが行われてきたこと，さらには海外のような腫瘍内科医が育成されなかったことなどによると考えられる．臨床現場の多忙や静注治療を実施するための外来治療センターなどの基盤整備が不十分であったことから，抗癌薬治療の主役は静注抗癌薬よりも経口抗癌薬にならざるをえなかったのはやむをえない．結果的に世界的にももっとも経口抗癌薬の臨床経験に富む国となった．しかしながら，経口抗癌薬の表面的な利便性や有害事象が少ないというイメージのみが先行し，臨床的意義である生存期間や無再発生存期間などの評価項目での臨床評価が遅れてしまった．UFTやdoxifluridine，S-1あるいはcapecitabineなどの国内発の優れた経口抗癌薬の5-FU/LVとの大腸癌での直接比較であるRCTは海外において実施され，UFT/LVとcapecitabineの非劣性が検証されたのは最近のことである．この間に，大腸癌治療は再度静注治療法が主役となり，IFL，FOLFOX，FOLFIRIなど多忙な国内医療環境になじまない複雑な治療レジメンが標準治療と位置づけられるというジレンマを経験することになる．国内においてこれら静注治療法を導入しているあいだに海外ではcapecitabineの併用療法であるXELOX(capecitabine＋oxaliplatin)療法が積極的に評価され，転移性大腸癌ではXELOX療法とFOLFOX4療法の非劣性が検証されている．すなわち，経口抗癌薬の併用療法が静注療法に置き換え可能であるという証明がされたのである．経口抗癌薬の先進国であった日本が，結果としてその長所を生かすことなく欧米の後追いをしている現実はきわめて残念である．今後は，経口抗癌薬の長所をさらに伸ばすために術後補助療法での評価が実施されることになることが予想される．この点で，ACTS-GC試験により胃癌術後補助療法におけるS-1の臨床評価が国内で実施完了したこと

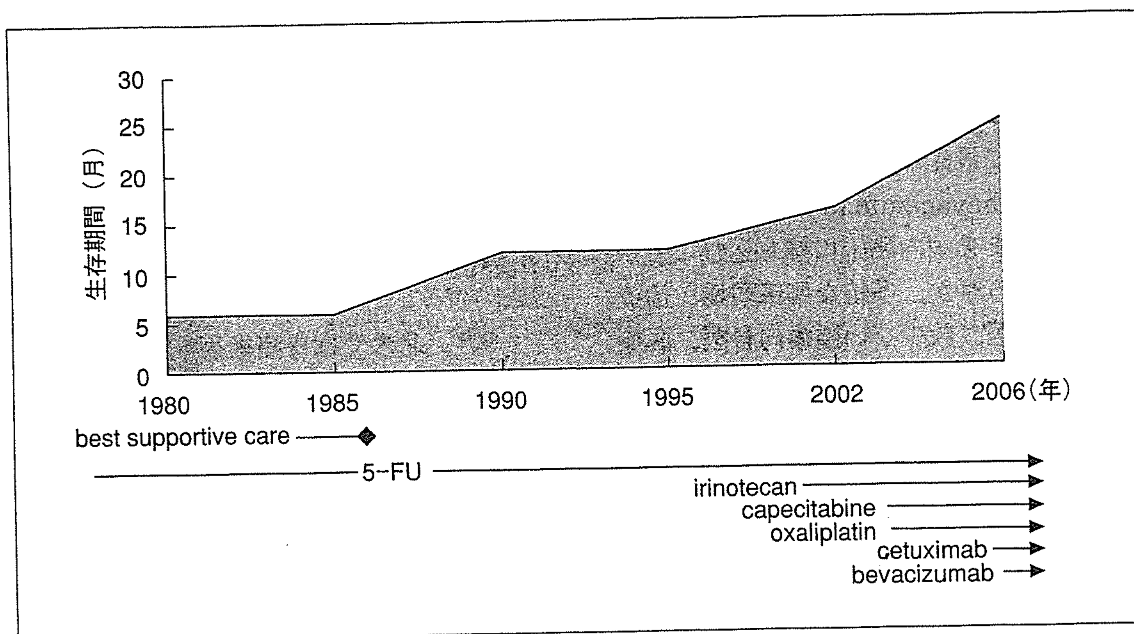

図1．転移性大腸癌治療成績の進歩．新薬登場と生存期間の延長

は特筆すべき快挙である．長期的戦略のもとに，全国規模で臨床試験を展開すれば十分国際的に評価される臨床試験を実施できるのである．このような実績をもとに，海外との国際共同試験における主要メンバーとしての参加が可能となると考えられる．

Ⅴ 新規薬剤の臨床的意義(図1)

大腸癌治療を例にとると2005年のoxaliplatin承認以降，新規抗癌薬であるbevacizumabやcetuximabなどに多くの期待が寄せられている．患者数を考慮すると乳癌に対するtrastuzumabやリンパ腫に対するrituximab以上のインパクトが予想される．すでに多くの海外臨床成績が報告され，一次治療，二次治療での有効性や，5-FU/LV，IFL，FOLFOX4などの基本抗癌薬治療との併用の組み合せでの有効性が確認されているbevacizumabではさらに大きな期待が寄せられている．このような分子標的治療薬や抗体医薬品は新しい治療の可能性を開拓した点では大きな進歩である．癌の生物学的特徴の解析が臨床で開花したともいえる．しかしながら，その特異的な作用機序のために従来経験したことのない有害事象が報告されている．高血圧，腸管穿孔，血管塞栓などである．頻度は必ずしも高くはないが，経験がない事象ではしばしば発見，対応が遅れることがあるので十分に観察する必要がある．また，臨床的な有用性が認められた患者集団を再度確認する必要がある．治療抵抗性となった全身状態不良の患者に対する魔法の薬でないことは明らかである．適応対象を慎重に選択し，標準投与量をスケジュールに従い投与し，有害事象の発現に応じて適切に減量，休薬を実施することにより最大限の治療効果を実現できるのである．もちろん，併用される抗癌薬治療レジメンも今までの臨床試験成績を参考に，標準的投与量で実施すべきである．安全性を優先して，低用量で実施することで期待される有効性を実現することは一般に不可能である．また，分子標的治療薬は有害事象がなく，長期間腫瘍増大をきたさないという当初のキャッチフレーズは現在では受け入れられていないので，使用に関しては十分な知識が必要となる．

Ⅵ 先行する海外臨床試験の国内導入

海外臨床試験成績が海外学会やインターネットなどで先行発表される時代となり，国内臨床現場での混乱がみられる．国内メディアの偏向報道にも一因がある．毒性や医療費に関するマイナス面

に関する報道が不十分である．臨床医は，臨床試験成績を包括的に概観し，新治療によるベネフィットとリスクについて十分に自ら理解しなければならない．常に最先端には未知のリスクが伴う．すでに述べたbevacizumabに関しても，海外臨床成績をそのまま国内臨床に持ち込むことが現実的に可能であろうか．多忙な臨床現場，治療の主体を担う外科医，数少ない腫瘍内科医，医療費への無関心など多くの国内医療環境の問題点がある．海外との医療レベルを比較することは，国内での医療格差を考慮すればむずかしいことは容易に理解できるが，国内の標準的医療をどのレベルに求めるかは医療関係者のみならず，患者や医療費支払機関，さらには国民の合意が必要な大きな問題である．欧米と同様の最先端医療を享受したいのは患者の希望である．しかし，海外では医療を受けることのできない患者も多数おり，国家単位の医療レベルでは日本は決して低い国ではない．いわゆる先進医療をどの程度，どの時期に，誰が負担して国内導入に踏み切るか，最近の新規有効抗癌薬が登場したこの時期にこそ十分な議論が必要と考える．

Ⅶ 異なる国内医療環境における新治療の適応

国内の癌治療はX線検査，内視鏡検査，病理検査などの診断学，外科治療学を中心に臓器ごとに進歩してきた．この結果，治療成績はきわめて順調に向上してきたのも事実である．しかしながら対照的に，転移，再発癌患者の治療成績の進歩がみられないことも明らかとなった．

このような中，海外を中心に臨床評価された新規抗癌薬の登場により転移・再発癌の治療成績は着実に向上している．新規薬剤を国内導入するさいには，海外と比較して診断学，外科治療学の進歩している国内環境が大きなアドバンテージを有していることは明らかである．

ACTS-GCによる胃癌の術後補助療法やNSAS-CCおよびTAC-CRによる直腸癌の術後補助療法の成績は国内の優れた外科手術と，多くの切除リンパ節を検索してくれる病理医の共同作業が基礎にある．残念ながら海外では数施設以外に国内医療を再現することはむずかしいであろう．

一方，北米では胃癌術後補助療法は化学放射線療法であり，大腸癌術後補助療法がoxaliplatin併用のFOLFOX療法に移行している状況をみると，癌治療は診断，外科，抗癌薬治療(放射線治療)の集学的治療のたまものと再認識する．

治療戦略が異なる領域や，臨床試験が実施可能な領域では，国内環境への導入の可否につきなんらかの臨床試験で確認していく必要があると考えている．保守的な考えとの批判はあるが，臨床医として「エビデンスと経験」に基づいた医療を患者に提供するためには，海外データの直輸入には抵抗を感じてしまう．

臨床試験により多くのエビデンスが創生され構築された．治療成績が進歩したことも事実である．しかし，大多数の臨床現場でその事実を再現し，治療の進歩を患者に提供するためには，臨床医には多くの仕事が残されている．

おわりに

最近の抗癌薬治療の進歩は目覚ましい．これらは多くの海外臨床試験成績に基づくものである．患者は最善の治療効果を期待するのは当然であり，臨床医はそれに応える努力が必要である．しかし，医療の現場は日本国内の医療現場である．海外での治療進歩を目の前の癌患者でいかにして再現するかはまだ多くの問題を抱えているが，多くの臨床医が着実な進歩を実感しているのも事実である．第一線の臨床医が抗癌薬治療に精通して治療成績を向上することにおおいに期待したい．

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特集 変わってきた癌化学療法

大腸癌の化学療法

Systemic chemotherapy for metastatic colorectal cancer in 2006

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切除不能転移性大腸癌に対する化学療法は，1990年代後半から10年足らずの間に大きな進歩が見られている．長年のKey Drugであった5FUに加え，新規薬剤としてCPT-11やoxaliplatinが臨床導入され，さらに経口抗癌剤の臨床評価により，簡便性，安全性が客観的に検証された．最近では分子標的治療薬の大腸癌における有用性が示されることになり，切除不能転移性大腸癌の生存期間は無治療の8ヵ月から今や2年を超える時代となった．臨床現場では適切な薬剤選択と治療継続の判断を行うことがますます重要となっている．国際的標準治療の変化を常にフォローしながら，最善の治療法を患者に提供することが求められている．

はじめに

国立がんセンターホームページに掲載されている「がんの統計'05」[1]によると，本邦における結腸・直腸癌の年齢調整死亡率(2003年)は男性で肺癌，胃癌，肝臓癌に次いで4番目，女性ではついに胃癌を抜き1番目となっている。大腸癌による年間死亡者数は2005年には年間3.9万人であったが，2015年には6万人にのぼると推定されている。大腸癌治療の中心はあくまで外科的切除であるが，一方で外科的切除によって治癒し得ない，いわゆる切除不能転移性大腸癌の治療法の確立と普及が本邦において急務となっている。

本稿では，切除不能転移性大腸癌に対する化学療法につき解説する。

I. 切除不能転移性大腸癌に対する化学療法の適応

切除不能転移性大腸癌の予後はBSC(best supportive care)群では8ヵ月とされ，化学療法により12ヵ月に延長することが可能であるというメタアナリシスの報告がある[2]。これを根拠として，全身状態のよい症例では，積極的に化学療法を行うことが勧められている。大腸癌では，切除不能転移病巣を有する症例においても自覚症状や臨床検査値異常を認めることは少なく，食欲不振，下痢，悪心・嘔吐，白血球減少などの化学療法に伴う有害事象による全身状態の一過性の低下との兼ね合いで治療を考慮する必要がある。なお，骨転

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