表V-1-9　治療回数，個数

	MCT	RFA	p-value
1回	22 (46.8%)	45 (67.2%)	N.S.*
2回	9 (19.1%)	13 (19.4%)	
3回	4 (8.5%)	3 (4.5%)	
4回	1 (2.1%)	3 (4.5%)	
5回以上	9 (19.1%)	3 (4.5%)	
不明	2 (4.3%)	0	

	MCT	RFA	p-value
中央値	1.5	1	N.S.*
1個	18 (38.3%)	38 (56.7%)	
2個	7 (14.9%)	12 (17.9%)	
3個	4 (8.5%)	3 (4.5%)	
4個	1 (2.1%)	3 (4.5%)	
5個	2 (4.3%)	3 (4.5%)	
6個以上	4 (8.5%)	0	
不明	11 (23.4%)	8 (11.9%)	

*：Mann-Whitney's test　　N.S.：no significant

表V-1-10　凝固療法を施行した転移巣区域

	MCT	RFA
1区域	21 (44.7%)	31 (46.3%)
2区域	14 (29.8%)	19 (28.4%)
3区域	7 (14.9%)	11 (16.4%)
4区域	3 (6.4%)	4 (6.0%)
不明	2 (4.3%)	2 (3.0%)

<1区域>

	MCT	RFA
A（前区域）	10 (21.3%)	10 (14.9%)
P（後区域）	4 (8.5%)	9 (13.4%)
M（内側区域）	2 (4.3%)	6 (9.0%)
L（外側区域）	5 (10.6%)	5 (7.5%)
C（尾状葉）	0	1 (1.5%)

<2区域>

	MCT	RFA
A+P	2 (4.3%)	6 (9.0%)
A+M	0	2 (3.0%)
A+L	4 (8.5%)	2 (3.0%)
P+M	1 (2.1%)	1 (1.5%)
P+L	3 (6.4%)	5 (7.5%)
P+C	1 (2.1%)	1 (1.5%)
M+L	3 (6.4%)	2 (3.0%)

<3区域>

	MCT	RFA
A+P+M	0	7 (10.4%)
A+P+L	2 (4.3%)	1 (1.5%)
A+M+L	1 (2.1%)	2 (3.0%)
P+M+L	3 (6.4%)	0
P+L+C	1 (2.1%)	0
M+L+C	0	1 (1.5%)

<4区域>

	MCT	RFA
A+P+M+L	3 (6.4%)	3 (4.5%)
A+M+L+C	0	1 (1.5%)

表V-1-11　アプローチ

	MCT	RFA	p-value
経皮的	13 (27.7%)	36 (53.7%)	
開腹的	31 (66.0%)	28 (41.8%)	p=0.006*
不明	3 (6.4%)	3 (4.5%)	

*：Fisher's exact probability test

表V-1-12　同時併用療法の種類

	MCT	RFA	p-value
肝切	18 (38.3%)	17 (25.4%)	
全身化学療法	8 (17.0%)	15 (22.4%)	
肝動注	5 (10.6%)	7 (10.4%)	
塞栓術	0	2 (3.0%)	N.S.*
免疫療法	1 (2.1%)	0	
PEIT	0	1 (1.5%)	
不明	15 (31.9%)	25 (37.3%)	

*：Mann-Whitney's test　N.S.：no significant

表V-1-13　治療効果

＜I．治療部位の肝転移遺残＞

	MCT	RFA	p-value
なし	29 (61.7%)	48 (71.6%)	
あり	14 (29.8%)	17 (25.4%)	N.S.*
不明	4 (8.5%)	2 (3.0%)	

＜II．全体の奏効度＞

	MCT	RFA	p-value
CR	21 (44.7%)	35 (52.2%)	
PR	7 (14.9%)	11 (16.4%)	
NC	4 (8.5%)	5 (7.5%)	N.S.*
PD	8 (17.0%)	1 (1.5%)	
不明	7 (14.9%)	15 (22.4%)	

*：Mann-Whitney's test　N.S.：no significant
CR：Complete Response, PR：Partial Response,
NC：No Change, PD：Progressive Disease

表V-1-14　腫瘍マーカーの変化（中央値）

＜CEA値（ng/m*l*）＞

	MCT	RFA
当該治療前	11.3	10.5
治療1カ月後	3.2	13.7
治療3カ月後	4.9	15.7

＜CA 19-9値（U/m*l*）＞

	MCT	RFA
当該治療前	29	18.7
治療1カ月後	27	21.8
治療3カ月後	28	18.1

表V-1-15　合併症

	MCT	RFA	p-value
なし	42 (89.4%)	54 (80.6%)	
あり	5 (10.6%)	7 (10.4%)	N.S.*
不明	0	6 (9.0%)	

＜合併症の種類＞

	MCT	RFA	p-value
膿瘍形成	1 (20.0%)	2 (28.6%)	
胆汁漏	2 (40.0%)	0	
肝機能障害	1 (20.0%)	0	
アレルギー	0	1 (14.3%)	N.S.*
気胸	0	1 (14.3%)	
創感染	0	1 (14.3%)	
不明	1 (20.0%)	2 (28.6%)	

*：Mann-Whitney's test　N.S.：no significant

表V-1-16　肝転移状況と治療効果

<MCT>

	肝転移個数	大きさ(cm)	転移区域数	肝切除の状況		前治療の有無	
肝転移遺残				可能	不可能	なし	あり
なし	2.8±0.4(n=28)	2.3±0.2(n=27)	1.8±0.2(n=28)	19(40.4%)	9(19.1%)	15(31.9%)	14(29.8%)
あり	3.5±0.8(n=13)	3.2±0.8(n=13)	2.1±0.2(n=14)	7(14.9%)	7(14.9%)	9(19.1%)	5(10.6%)
全体の奏効度							
CR	3.0±0.5(n=21)	2.2±0.1(n=19)	1.8±0.2(n=21)	13(27.7%)	7(14.9%)	12(25.5%)	9(19.1%)
PR	3.4±1.2(n=7)	3.6±1.3(n=7)	2.1±0.4(n=7)	4(8.5%)	3(6.4%)	7(14.9%)	0
NC	3.8±1.0(n=4)	2.1±0.4(n=3)	2.3±0.6(n=4)	2(4.3%)	2(4.3%)	0	4(8.5%)
PD	2.6±0.6(n=7)	2.8±1.0(n=8)	1.7±0.3(n=7)	4(8.5%)	4(8.5%)	4(8.5%)	4(8.5%)

<RFA>

	肝転移個数	大きさ(cm)	転移区域数	肝切除の状況		前治療の有無	
肝転移遺残				可能	不可能	なし	あり
なし	2.1±0.2[a](n=48)	3.8±0.8(n=48)	1.6±0.1[g](n=46)	37(55.2%)	9(13.4%)[#]	20(29.9%)	27(40.3%)
あり	3.6±0.6[b](n=17)	3.3±0.2(n=17)	2.4±0.3[h](n=17)	6(9.0%)	10(14.9%)	3(4.5%)	13(19.4%)
全体の奏効度							
CR	1.9±0.2[c](n=35)	3.3±0.8(n=35)	1.5±0.1[i](n=34)	25(37.3%)	8(11.9%)	16(23.9%)	18(26.9%)
PR	3.7±0.7[d](n=11)	3.5±0.3[e](n=11)	2.4±0.4[j](n=11)	3(4.5%)	7(10.4%)	3(4.5%)	7(10.4%)
NC	2.4±0.5(n=5)	2.3±0.6[f](n=5)	2.4±0.5[k](n=5)	3(4.5%)	2(3.0%)	1(1.5%)	4(6.0%)
PD	8(n=1)	2.9(n=1)	3(n=1)	0	1(1.5%)	0	1(1.5%)

a, b：p=0.0046, c, d：p=0.0015, e, f：p=0.0456, g, h：p=0.0013, i, k：p=0.0041
i, j：p=0.0156, [#]：p=0.0018
転移区域数は前区域，後区域，内側区域，外側区域，尾状葉の5区域とした．
肝転移遺残および全体の奏効度の記載のない症例は省いてある．

9．熱凝固療法を施行した転移巣の区域

熱凝固療法を施行した転移巣の区域は，MCT，RFAともに1区域がもっとも多く，領域としてはA(前区域)が多かった．2区域以上でも，A(前区域)またはP(後区域)が多かった(表V-1-10)．

10．アプローチ

治療経路はMCTでは開腹アプローチが経皮的アプローチより多いのに対して，RFAは経皮的アプローチのほうが多かった(p=0.006)(表V-1-11)．

11．同時併用療法

同時併用療法は，MCT，RFAともに肝切がもっとも多く，次いで全身化学療法，肝動注であった．そのほかに塞栓術，PEIT，免疫療法であった(表V-1-12)．

12．治療効果および予後

局所の治療効果は，MCT，RFAともに6割以上で肝転移遺残を認めず，全体の奏効率としては約半数がCRと評価されていた(表V-1-13)．

しかし，腫瘍マーカーの変化は，MCTではCEA値が術後正常値まで下降しているのに対し，RFAでは術後の値が術前より上昇していた．CA 19-9値は，MCT，RFAともに治療前後とも正常範囲内であった(表V-1-14)．

MCTの3年生存率は47.7%，5年生存率は

表V-1-17　施行方法と治療効果

＜MCT＞

	出力（ワット）	回数	時間（分）	経路		同時併用療法	
肝転移遺残				経皮	開腹	なし	あり
なし	68±3	5.0±1.3	0.9±0.03	7 (14.9%)	19 (40.4%)	11 (23.4%)	18 (38.3%)
あり	72±4	2.9±0.8	1.1±0.33	6 (12.8%)	8 (17.0%)	5 (10.6%)	9 (19.1%)
全体の奏効度							
CR	72±7	4.8±1.3[c]	1.9±1.01	5 (10.6%)	15 (31.9%)	7 (14.9%)	14 (29.8%)
PR	64±7[a]	1.6±0.4	1.7±0.75	2 (4.3%)	4 (8.5%)	4 (8.5%)	3 (6.4%)
NC	84±6	1.4±0.2[d]	1.1±0.13	2 (4.3%)	2 (4.3%)	1 (2.1%)	3 (6.4%)
PD	93±3[b]	9.5±4.2[e]	1.0±0.00	3 (6.4%)	4 (8.5%)	3 (6.4%)	5 (10.6%)

a, b：p=0.0140, c, d：p=0.0448, d, e：p=0.0435

＜RFA＞

	出力（ワット）	回数	時間（分）	経路		同時併用療法	
肝転移遺残				経皮	開腹	なし	あり
なし	60±4[a]	1.9±0.3	13.4±2.2	23 (34.3%)	24 (35.8%)	22 (32.8%)	26 (38.8%)
あり	76±4[b]	1.6±0.2	17.5±2.9	11 (16.4%)	4 (6.0%)	10 (14.9%)	7 (10.4%)
全体の奏効度							
CR	59±4[c]	2.0±0.3	13.7±2.4	21 (31.3%)	14 (20.9%)	22 (32.8%)	13 (19.4%)
PR	82±3[d]	1.6±0.2	19.3±3.7	6 (9.0%)	4 (6.0%)	7 (10.4%)	4 (6.0%)
NC	76±3	1.2±0.2	11.1±2.6	5 (7.5%)	0	1 (1.5%)	4 (6.0%)
PD	—	—	—	0	0	1 (1.5%)	0

a, b：p=0.025, c, d：p=0.004

肝転移遺残および全体の奏効度の記載のない症例は省いてある．

22.5%で，RFA ではそれぞれ 38.8%と 19.9%で，両者に差を認めなかった（p=0.60）．

13．合 併 症

MCT, RFA ともに 1 割程度の合併症があり，膿瘍形成，胆汁漏などを認めた（表V-1-15）．

14．肝転移状況および実際の施行方法と治療効果（肝転移遺残，奏効度）との関係

表V-1-16，17 に肝転移状況および実際の施行方法と治療効果（肝転移遺残，奏効度）との相関を示す．肝転移状況には転移個数，大きさ，転移肝区域数，肝切除可能性の有無，前治療の有無を，施行方法では出力（ワット），回数，時間（分），経路，同時併用療法を取り上げた．その結果，肝転移状況においては，MCT の場合，転移個数が 3.0 以下であると肝転移が遺残する危険性は少なかった．ただし，奏効度 PD 例の転移個数が 2.6 であった理由は，治療した肝転移巣以外の病巣進展のためである．また大きさが 3 cm または転移区域数が 2 区域を超えると肝転移が遺残していた．肝切除可能例では遺残の可能性が低く，同時に CR 率，PR 率が高かった．前治療の有無は治療効果とは関係がなかった．

RFA では，転移個数が少ない症例ほど，CR が多かった．また大きさは奏効度とは関係なかった．転移区域は 2 区域までが奏効度が良好であった．肝転移状況は MCT と同様，肝切除可能例では遺残の可能性が低く，同時に CR 率，PR 率が高かった．

施行方法と治療効果の関係では，MCT では

出力とは関係なかった．また施行回数が多いものほど，奏効度が良好であった．時間，同時併用療法はいずれも関係を認めなかった．しかし，開腹経路のほうが，治療効果が良好であった．またRFAでは，肝遺残を認めた症例ほど，出力が高かった．回数，時間，経路，同時併用療法はいずれも関係を認めなかった．

Ⅳ 考　察

マイクロ波は電磁波の一種で，周波数1～30 GHz，波長30 cm～1 mのものをいう．水やアルコールのような誘導物質は通過するが，有極性物質では分子運動が生じ摩擦熱が発生する．マイクロ波を腫瘍などに収束的に照射させると，熱変性してしまうのがこの治療の原理である[9]．また，ラジオ波も電磁波の一種で，周波数450 kHzのラジオ波を照射して誘電熱を発生させ，熱変性させることにより治療に用いる．マイクロ波とほぼ同じ原理である[10),11)]．しかし，ラジオ波はマイクロ波に比較して周囲組織のインピーダンスの上昇が少なく，広い範囲を均一に焼灼でき，また低温侵襲性で，血管損傷は穿刺時損傷以外ほとんどないとされている[12)]．

これらの熱凝固療法は元来，肝細胞癌に施行され肝切除に匹敵する治療と評価されており，その適応基準が確立している[13),14)]．MCTでは腫瘍径が2～3 cm以下で，ことに15 mm以下では治療効果が良好である．RFAでは3 cm，3個以下あるいは最大径5 cm以下単発腫瘍が適応基準とされている．しかし，大腸癌肝転移に関しては，適応基準は定まっていない．別府ら[15),16)]の適応は，①超音波検査またはCTで腫瘍が同定可能，②腫瘍個数の制限なし，③腫瘍径は5 cm以下とし，肝門部脈管近接例，腫瘍塞栓を有する症例，肝機能高度低下例，高度の出血傾向を認める例は除外としている．またMCTとRFAの使い分けについては，①経皮的アプローチではRFAが第一選択，②2 cm以下の腫瘍ではRFA，③2 cm以上の腫瘍ではMCT，と提唱している．

今回の検討から，本法の肝転移治療上問題となる以下の3点について考察する．

1．MCTとRFAの使い分け

治療効果（表Ⅴ-1-13），合併症（表Ⅴ-1-15），肝転移状況および実際の施行方法と治療効果（肝転移遺残，奏効度）との関係（表Ⅴ-1-16，17）では，両者間では有意な差を認めないことから，利点，欠点は今回の結果から言及することはできない．しかし，治療経路（表Ⅴ-1-11，17）では，有意差をもって，RFAでは経皮的アプローチが多く，別府ら[15),16)]の提唱とも一致しており，開腹ができない症例にはRFAを第一選択とすべきであると考えた．ただし，1990年代初期のころはRFAが普及しておらず，MCTが中心的であったが，近年RFAに対しても保険適応が認められたことから，最近ではRFAがMCTよりも行われる頻度が高くなったものと考えられる．

2．安全性

肝細胞癌に対してはMCTでは5～14.2%，RFAでは10～12%の合併症が認められると報告されている[13)]．今回の結果ではMCTでは10.6%，RFAでは10.4%であり，大腸癌肝転移に施行した場合でも合併症の頻度は同じ程度であり，現段階では合併症の少ない安全な治療法であると考える．しかし，肝細胞癌に対してはMCTの場合，4 cmを超えると合併症の頻度が有意に高くなるとも報告されている[13)]．今後，大腸癌肝転移に対して熱凝固療法がますます普及していき，同時に適応範囲が拡大すると思われるが，従来の適応を外れて使用する場合には予想外の合併症に十分注意して行う必要がある．

3．将来への展望

肝切除を行わなくても，局所のCRが期待で

きる治療法である熱凝固療法を駆使することにより，肝転移巣を可及的にコントロールすることが大腸癌症例の予後のさらなる改善につながる．MCTの3年生存率は48%，5年生存率は23%，RFAは39%と20%である．これは肝切除の53%，39%よりは悪いが，肝動注の12%と6%よりは良好であり[17]，生存率から判断して，MCT，RFAは肝切除にとってかわるまでには至っていないが，肝動注よりは有効である．現時点での大腸癌肝転移に対する治療の選択は，肝切除＞熱凝固療法（MCT，RFA）＞肝動注療法の順であると考える．

おわりに

今回の検討の対象は2003年までに治療された症例である．現在では熱凝固療法は当時より普及しており，大腸癌肝転移に対する重要な治療手段の一つになったと考える．今後，肝切除，肝動注療法，化学療法などの治療法と組み合わせることで治療成績が向上することを期待する．

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Extramural Cancer Deposits Without Nodal Structure in Colorectal Cancer

Optimal Categorization for Prognostic Staging

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Key Words: Colorectal cancer; Prognostic staging; Lymph node metastasis; Cancer deposits; TNM classification

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Abstract

To establish an optimal categorization of cancer deposits without lymph node structure (extranodal cancer deposits [EX]) in a prognostic staging system, we analyzed 1,027 cases in which patients underwent potentially curative surgery for advanced colorectal adenocarcinoma. EX was classified as vascular invasion-type (VAS) or non-VAS.

A total of 512 foci of EX were identified in 205 patients (20.0%), with VAS and non-VAS found in 68 and 182 patients, respectively. The hazard ratio for patients with nodal involvement was 3.6 and for patients with VAS and non-VAS, 2.5 and 4.7, respectively. Based on multivariate analysis of these 3 parameters, only nodal involvement and non-VAS were significant prognosticators. By using the Akaike information criterion, N staging was capable of predicting survival outcome with the highest accuracy when both nodal involvement and non-VAS were treated together as an N factor and VAS was treated as a T factor ("new categorization"). The clinical significance of the TNM grading system for colorectal cancer would be enhanced if we treat EX as a new categorization.

The TNM classification is used worldwide for cancer staging. For patients who have undergone curative resection of colorectal cancer without distant metastasis, the clinical stage is determined based on 2 parameters: tumor penetration depth (T factor) and number of involved nodes (N factor). Several prognostic classifications have been reported since the 1930s when Dukes[1] proposed a prognostic classification of cancer of the rectum, but the T and N factors have been confirmed to be the "gold standard" parameters in a number of studies.[2-6]

Lymph node involvement is a representative histologic feature of indirect regional cancer spread, but there are cancer deposits that show no histologic evidence of lymph node structure in the mesorectum or mesocolon; it has long been ambiguous whether such involvement should be treated as a T factor or an N factor or should be excluded from consideration in determining tumor stage.[7] In the *TNM Classification of Malignant Tumours*, 5th edition,[8] the treatment of a tumor nodule without histologic evidence of a regional lymph node in the nodule was first proposed; a tumor nodule greater than 3 mm in diameter is classified in the N category as lymph node metastasis, whereas a nodule up to but not exceeding 3 mm in diameter is classified in the T category as a discontinuous extension.[8] However, the criterion of categorization of this type of cancer spread changed in the 6th edition,[9] which recommends that a tumor nodule be classified in the N category if the nodule has the form and smooth contour of a lymph node and in the T category if the nodule has an irregular contour.[9] To date, few studies have addressed this issue through prognostic analysis in colorectal cancer, and there are few data on the optimal categorization of such foci. Nevertheless, an optimal categorization should heighten the value of the TNM classification as a prognostic grading system.

In the present study, we reviewed tumor deposits showing no histologic evidence of lymph node structure observed based on routinely processed lymphadenectomy specimens (extranodal cancer deposits [EX]), classifying them into several types based on their morphologic features. We also compared the respective prognostic weight of the various features. The goals of the present study were to determine how EX should be categorized in the prognostic staging system and to identify an EX-related parameter that could provide useful prognostic information.

Materials and Methods

Cases

We reviewed the cases of 1,027 patients (601 men, 426 women; median age, 61.9 years; age range, 21-91 years) who had undergone potentially curative surgery for advanced colorectal cancer at the National Defense Medical College Hospital (Saitama, Japan) between January 1980 and December 1999. The tumors were pathologically confirmed to be adenocarcinomas invading into or through the muscularis propria. We identified colon cancers in 512 cases (cecum, 48; ascending colon, 108; transverse colon, 56; descending colon, 44; and sigmoid colon, 256) and 515 cases were rectal cancer (rectosigmoid, 151; rectum above the peritoneal reflection, 128; and rectum below the peritoneal reflection, 236). The surgical procedures performed were the following: colectomy, 500; anterior resection, 308; abdominoperineal resection, 180; total pelvic resection, 22; and Hartmann procedure, 17.

All patients were followed up for at least 5 years or until death. The mean follow-up period of survivors was 96 months. No patients received preoperative adjuvant therapy. With regard to postoperative adjuvant therapy, no patients received systemic intravenous chemotherapy or radiation therapy, but most patients were given oral chemotherapeutic agents such as 5-fluorouracil, 5'-doxifluridine, carmofur, or uracil-tegafur at the attending surgeon's discretion for around 6 to 12 months. All clinicopathologic data for tumors, including follow-up status, were obtained from clinical or pathology records.

Determination of EX and Its Pathologic Classification

Specimens delivered to pathologists for the examination of lymph node metastasis were collected fresh by surgeons as follows: the peritoneum overlying the remainder of the mesentery was incised and examined by careful palpation for the presence of lymph nodes. The mesenteric fat was carefully displaced by manual pressure, visually inspected for lymph nodes, and palpated for the presence of firm tissue indicative of a lymph node or tumor nodule. This procedure ranged to the peritumoral fatty tissue within the limits allowed while maintaining a circumferential surgical margin. Any firm tissue remaining after gentle pressure on the fatty tissue was isolated from the surrounding mesenteric fat and sent as a lymph node specimen for histologic examination. Histologic sections were processed in the usual manner, cut at a thickness of 4 μm, and stained routinely with H&E. In the examined pathology reports, the average number of lymph nodes collected and examined for metastasis per patient was 21.9 in colon cancer cases and 29.8 in rectal cancer cases.

All pathology specimens obtained by the aforementioned procedure were reviewed by one of us (H.U.), and metastatic foci were classified into distinct lymph node metastases and cancer foci having no histologic evidence of lymph node structure (EX). Isolated cancer foci observed in fatty tissue attached to lymph nodes were treated as EX, irrespective of the nodal state, although extracapsular direct extension of the tumor was classified in nodal involvement. The maximum diameter of EX was measured on the slide. EX was divided into 2 types: EX with smooth contours, indicating that it originated in lymph node metastasis, and EX with irregular contours, according to the TNM definition (6th edition).[9]

In addition, EX was classified into the foci mostly confined to a vascular (lymphatic or venous vessel) space (vascular invasion type [VAS]) and cancer foci other than vascular invasion (non-VAS) **Image 1**. Non-VAS developing into a tumor nodule accompanied by venous and/or neural invasion in its actively invasive region was designated as aggressive EX **Image 2**.

Statistical Analyses

Statistical analyses were performed using SPSS software (SPSS, Chicago, IL). Correlations between EX and other clinicopathologic factors were estimated by using the χ^2 test, the Mann-Whitney *U* test, or a Student *t* test. Univariate and multivariate analyses using the Cox proportional hazards model were carried out to estimate the impact of various parameters on postoperative cancer-related survival. The Akaike Information Criterion (AIC)[10] was used to identify the optimal categorization of EX that afforded the N and T stages the highest power of discrimination of survival outcome. The AIC (AIC = −2 × Log Likelihood + 2 × No. of Parameters in the Model) is an estimate of the measure of fit of a model to a given set of data. The model of choice achieves parsimony with maximum likelihood and is the one with the lowest value of AIC, indicating the smallest loss of information for predicting outcome.[11]

Results

Incidence of EX

A total of 512 foci of EX were detected in 205 patients (20.0%). The incidence of EX was significantly higher in the rectal cancer (120 cases [23.3%]) than in colon cancer (85

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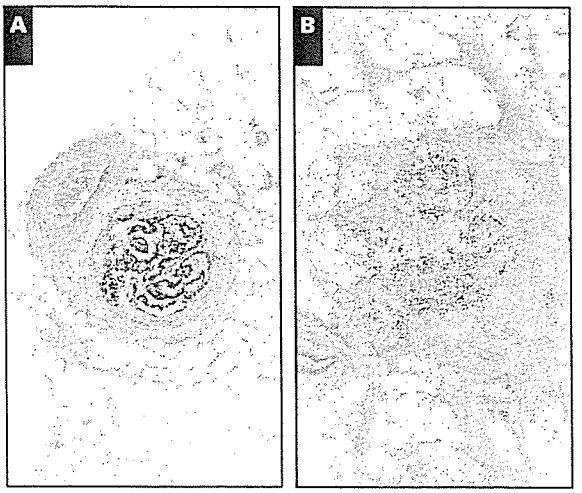

Image 1 Classification of extranodal cancer deposits (EX). **A**, Vascular invasion-type (VAS) EX (H&E, ×10). **B**, Non-VAS (H&E, ×2).

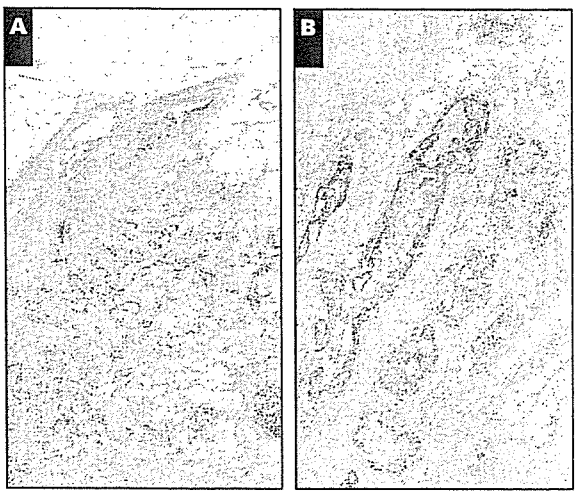

Image 2 Aggressive extranodal cancer deposits (EX). Aggressive EX was defined as non–vascular invasion-type EX developing into a tumor nodule in which venous invasion (**A**) or neural invasion (**B**) was observed in an actively invasive region (H&E, ×4).

cases [16.6%]) **Table 1**. In addition, the incidence of EX had a positive correlation with tumor penetration depth, which was determined by leaving the existence of EX out of the calculation. A total of 102 VAS foci were observed in 68 patients (6.6%), and 410 non-VAS foci were observed in 182 patients (17.7%). Aggressive EX was found in 69 patients (6.7%).

With respect to the contours of the tumor deposits, we found 98 smooth-type foci and 414 irregular-type foci **Table 2**. The size of tumor deposits did not differ significantly according to contour. On the other hand, the average size of non-VAS (6.4 mm) was much larger than that of VAS (1.6 mm); the average size of aggressive EX was particularly large at 11.1 mm.

Table 2
Size of Extranodal Cancer Deposits

Classification	No. of Foci	Mean ± SD Size (mm)	*P*
Contour			
Smooth	98	5.7 ± 3.6	.5659
Irregular	414	5.4 ± 5.0	
Type			
VAS	102	1.6 ± 2.0	<.0001*
Non-VAS	410	6.4 ± 4.8	
Aggressive	114	11.1 ± 4.6	

VAS, vascular invasion type.
* VAS vs non-VAS.

Table 1
Incidence of Extranodal Cancer Deposits

			Total No. (%) of EX Foci According to the Type of EX		
Variables	No. (%) of Patients With EX	*P*	VAS	Non-VAS	Aggressive EX
Tumor location					
Colon (n = 512)	85 (16.6)	.0072*	21 (4.1)	77 (15.0)	22 (4.3)
Rectum (n = 515)	120 (23.3)		47 (9.1)	105 (20.4)	47 (9.1)
Tumor penetration depth					
T2 (n = 156)	6 (3.8)	.0002†	1 (0.6)	5 (3.2)	1 (0.6)
T3 (n = 802)	180 (22.4)		60 (7.5)	161 (20.1)	62 (7.7)
T4 (n = 69)	19 (28)		7 (10.1)	16 (23.2)	6 (8.7)
No. with distinct nodal involvement					
0 (n = 607)	30 (4.9)	<.0001†	6 (1.0)	28 (4.6)	10 (1.6)
1-3 (n = 322)	111 (34.5)		39 (12.1)	98 (30.4)	34 (10.6)
≥4 (n = 98)	64 (65.3)		23 (23.5)	56 (57.1)	25 (25.6)

EX, extranodal cancer deposits; VAS, vascular invasion type.
* χ^2 test.
† Mann-Whitney *U* test.

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Prognostic Impact of EX

Based on the present Cox proportional regression analysis, patients with distinct nodal involvement had a hazard ratio (HR) of 3.6 when patients with no distinct nodal involvement were regarded as the standard. In the same manner, the HR of the presence of EX was calculated as 4.5, which was slightly higher than that of distinct nodal involvement **Table 3**. The type of contour of EX had no effect on postoperative survival; however, survival impact differed significantly with the size of EX **Figure 1**. The 5-year survival rate of patients with EX 10 mm or larger in diameter was only 37.8%. The HR of VAS was 2.5, and that of non-VAS was 4.7. Based on multivariate survival analysis using the Cox proportional hazards model, distinct nodal involvement and non-VAS were independent prognosticators, but the survival impact of the existence of VAS was much smaller than that of these 2 parameters **Table 4**.

Table 3
Prognostic Impact of Extramural Cancer Spread Based on Cox Proportional Regression Analysis

Type of Extramural Cancer Spread	HR (95% CI)*	*P*
Nodal involvement	3.6 (2.6-4.8)	<.0001
Extranodal cancer deposits	4.5 (3.4-6.0)	<.0001
Contour		
Smooth	3.5 (2.4-5.1)	<.0001
Irregular	3.9 (2.9-5.2)	<.0001
Type		
VAS	2.5 (1.6-3.8)	<.0001
Non-VAS	4.7 (3.5-6.2)	<.0001
Aggressive	8.0 (5.8-11.2)	<.0001

CI, confidence interval; HR, hazard ratio; VAS, vascular invasion-type.
* Cases without respective type of extramural cancer spread were regarded as standard.

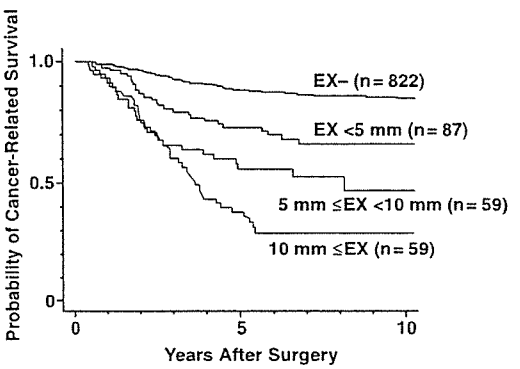

Figure 1 Impact of the size of the largest extranodal cancer deposit (EX) on postoperative cancer-related survival. The 5-y survival rates were as follows: EX–, 88.4%; EX <5 mm, 73.0%; EX 5 to <10 mm, 55.6%; and EX ≥10 mm, 37.8. EX– vs EX <5 mm, P <.0001; EX <5 mm vs 5 to <10 mm, P = .0336; EX 5 to <10 mm vs 10 mm ≤ EX, P = .0582.

Based on univariate analysis, the HR of patients with aggressive EX reached 8.0 when patients without it were regarded as standard (Table 3). As demonstrated in **Figure 2**, the presence of aggressive EX exerted a negative impact on survival, irrespective of number of nodes with distinct involvement.

EX and TNM Classification

The power to stratify cases with different survival outcomes based on the N stage (N0, N1, and N2) and the T stage (T2, T3, and T4) was compared among the following 5 definitions of the N and T categories: A, the TNM definition (5th edition)[8]; B, the TNM definition (6th edition)[9]; C, the provisional definition under which only distinct nodal involvement is treated as an N factor and EX is treated as a T factor; D, the provisional definition under which distinct nodal involvement and EX are treated as N factors; and E, the provisional definition under which distinct nodal involvement and non-VAS are treated as N factors and VAS is treated as a T factor **Table 5**.

Based on the value of AIC, the N stage having the lowest ability to stratify cases based on survival outcome was the definition under which only distinct nodal involvement was treated as an N factor (AIC = 2,576.5), followed by the definition of the 6th edition TNM (AIC = 2,572.7).[9] The definition under which distinct nodal involvement and non-VAS were treated as N factors and VAS as a T factor provided the best prognostic staging (AIC = 2,548.6) (Table 5). Distribution and 5-year survival rates of 1,027 patients in this series based on N stages by these 3 definitions are shown in **Figure 3**. The differences between the values of the T-stage among the aforementioned provisional definitions were much smaller than those between the values of the N stage (AIC = 2,640.7-2,642.6).

Discussion

The present study has 2 clinically important aspects: first, the optimal categorization of EX in a prognostic staging system by classifying it as VAS or non-VAS, and second, the unequaled value of aggressive EX as an indicator of very poor prognosis.

The existence of isolated tumor deposits in the mesorectum was well demonstrated by microscopic examination with serial transverse sections of the mesorectum made as reported by Scott et al[12] and Reynolds et al.[13] In routine practice, such tumor deposits are observed in specimens sent for pathologic examination as "lymph nodes." There are also terms relating to cancer deposits with no residual lymph node structure: "mesorectal deposit,"[12,13] "mesenteric implants,"[14] "extrabowel skipped cancer infiltration,"[15] "extranodal cancer deposit,"[16] "tumor nodule,"[8,9] and "pericolonic tumor deposits."[17] Paty et al[14] first showed the prognostic significance of such lesions;

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eg, mesenteric implants were reported to be associated with increased risk for pelvic recurrence in patients with rectal cancer who had undergone low anterior resection with coloanal anastomosis. Goldstein and Turner[17] believed that the number and greatest dimension of pericolonic tumor deposits should be reported separately from lymph node metastases.

We defined EX as all types of isolated cancer lesions having no residual lymph node structure observed in lymphadenectomy

Table 4
Multivariate Survival Analysis With Cox Proportional Regression Method

Parameters*	Coefficient	SE	χ^2	HR (95% CI)	*P*
Nodal involvement	0.853	0.171	24.788	2.3 (1.7-3.3)	<.0001
VAS	−0.066	0.230	0.082	0.9 (0.6-1.5)	.7749
Non-VAS	1.147	0.165	48.287	3.2 (2.3-4.4)	<.0001

CI, confidence interval; HR, hazard ratio; VAS, vascular invasion-type.
* Negative, 0; positive, 1.

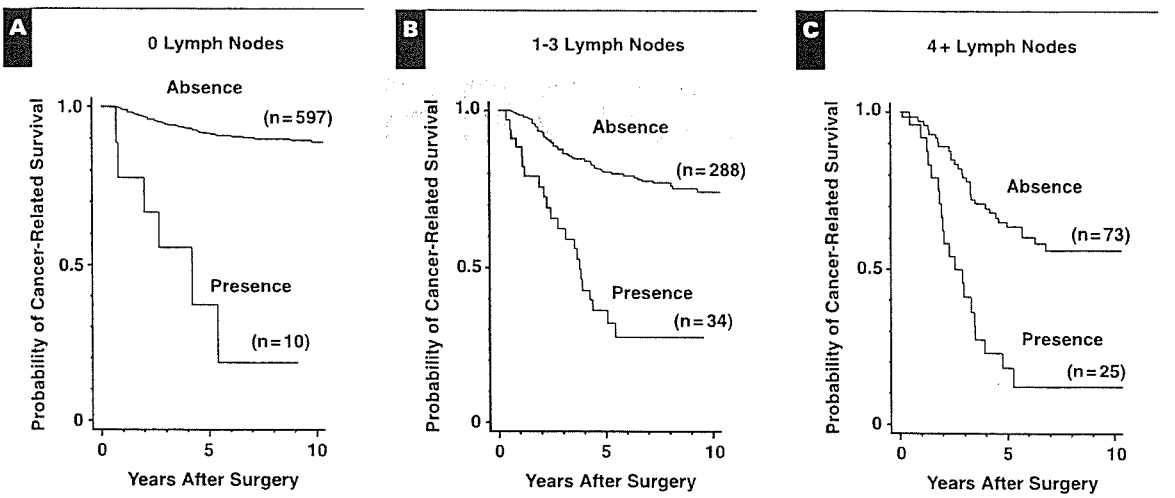

Figure 2 Impact of aggressive extranodal cancer deposits (EX) on postoperative cancer-related survival based on the number of lymph node metastases. The 5-y survival rates were as follows: **A**, Absence, 91.5%; presence, 37.0%. **B**, Absence, 80.3%; presence, 36.3%. **C**, Absence, 63.6%; presence, 18.2%. Absence, patients without aggressive EX; Presence, patients with aggressive EX; $P < .0001$ in respective comparison.

Table 5
Definitions of N and T Categories and Their Impact on the Prognostic Value of N and T Staging Systems

	Extramural Cancer Lesion Discontinuous With Main Tumor Classified in N and T Categories		N Staging*		T Staging†	
Definition	N	T	AIC	HR‡ (95% CI)	AIC	HR‡ (95% CI)
A	TNM classification (5th ed)[8]		2,549.7	2.8 (2.3-3.3)	2,641.7	2.3 (1.7-3.1)
B	TNM classification (6th ed)[9]		2,572.7	2.6 (2.1-3.1)	2,641.9	2.3 (1.7-3.1)
C	Distinct nodal involvement	EX	2,576.5	2.5 (2.1-3.0)	2,640.7	2.4 (1.7-3.1)
D	1. Distinct nodal involvement 2. EX	—	2,549.9	2.7 (2.2-3.2)	2,642.6	2.3 (1.7-3.1)
E	1. Distinct nodal involvement 2. Non-VAS	VAS	2,548.6	2.7 (2.3-3.2)	2,641.2	2.3 (1.7-3.2)

AIC, Akaike information criteria; CI, confidence interval; EX, extranodal cancer deposits; HR, hazard ratio; VAS, vascular invasion-type EX.
* N0 = 0; N1 = 1; N2 = 2.
† T2 = 0; T3 = 1; T4 = 2.
‡ Cox proportional regression analysis.

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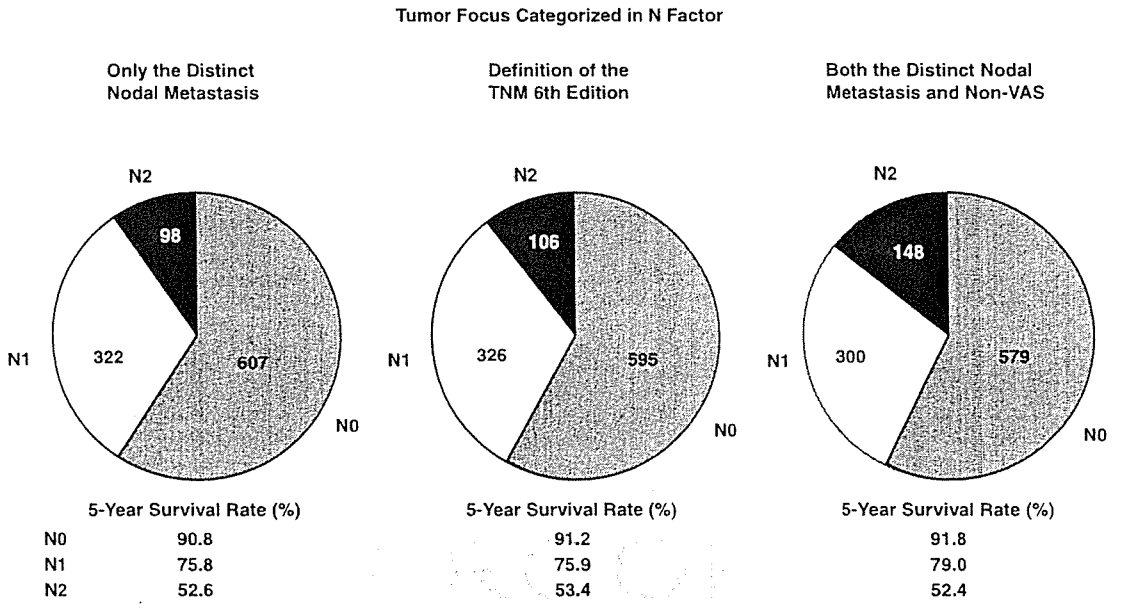

Figure 3 Distribution and 5-year survival rate of 1,027 patients based on N stages. Non-VAS, non–vascular invasion-type extranodal cancer deposits (EX). TNM 6th edition, see Sobin and Wittekind.[9]

specimens, ie, tumor deposits apparently not associated with lymph node involvement, tumor nodules that might be related to a ruined lymph node, and tiny cancer foci in the lymphatic channels, blood vessels, or perineural space.[15] In the present study, 20% of patients with advanced colorectal cancer who underwent potentially curative surgery were found to have EX; therefore, we cannot neglect the existence of EX in determining tumor stage. Ueno and Mochizuki[15] and Ueno et al[18] previously demonstrated that EX has clinical significance as a strong prognosticator independent of tumor depth or nodal involvement in patients with curatively resected advanced rectal cancer and in patients with colorectal cancer who underwent operation for lung metastasis.[16] However, in the present study, EX in patients with colorectal cancer was analyzed under the assumption that EX was treated as an N factor or as a T factor in a prognostic staging system.

We classified EX as VAS or non-VAS. Based on the present multivariate analyses using the Cox proportional hazards model, the prognostic impact of distinct nodal involvement and non-VAS was much higher than that of VAS. We compared 5 staging systems with different categorizations of EX, including categorizations based on the TNM classifications of the 5th and 6th editions[8,9] in terms of their discriminatory power with regard to survival outcome. In our analysis, we used the AIC,[10] which can be used to identify the optimal categorization of an outcome variable and to compare systems with different combinations of variables.[11,19,20] The power to stratify cases based on survival outcome was smallest when only distinct nodal involvement was treated as an N factor, followed by N staging as defined by the TNM 6th edition.[9] On the other hand, the value of AIC was smallest, ie, the value of prognostic staging was greatest, when distinct nodal involvement *and* non-VAS were treated as N factors and VAS was treated as a T factor (new categorization).

There was little difference in the 5-year survival rate of patients classified according to the various N staging systems shown in Figure 3. However, it was the new categorization described in the preceding paragraph that was found to be clinically most valuable. The clinically most beneficial grading system is one that assigns as many patients as possible to the most favorable or most unfavorable stage when survival outcome of patients classified in the same stage is the same.[21] It is noteworthy that the patient population classified in the N2 stage by the new categorization was 51% larger than the same population defined by N staging in which only distinct nodal invasion was regarded as an N factor and 40% larger than the population defined by N staging according to the TNM 6th edition.[9] In addition, objectivity is an advantageous characteristic of the new categorization compared with the TNM grading system now in use in which the contour of the foci is used as the primary criterion between N and T factors.

On the other hand, there was little difference in the AIC value among the T staging systems analyzed, and it could be said that the classification of EX exerts little influence on the clinical significance of the T stage because of the low incidence

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of EX in T2 cases, which was only 3.8% in the present series. With regard to the categorization as a "lymph node" of cancer foci having no residual lymph node structure in the specimen submitted for histologic examination, we concluded that we should divide EX into VAS and non-VAS categories, identifying the former as a T factor and the latter as an N factor. We believe that this definition will enhance the value of the TNM classification as a prognostic grading system, although it is important to verify its validity in other kinds of cancers.

Furthermore, the results of the present study underline the prognostic importance of aggressive EX. Tumor cells in aggressive EX, which have succeeded in their discontinuous spread, presumably through lymphatic or venous channels, and developed a tumor nodule, seem to be able to use new routes (blood vessels or the perineural space) for further development. The morphologic features of aggressive EX suggest that it could be a satellite lesion for systemic dissemination.

Although aggressive EX was observed in only 6.7% of our cases, it has the distinction of being an independent prognosticator of a very disappointing survival outcome (the 5-year survival rate of patients with aggressive EX was calculated at only 29.8%). Many pathologic parameters with prognostic significance, ie, cancer-related parameters (eg, tumor grade,[22] cancer growth pattern,[21] and tumor budding[6]) and host-related parameters (eg, tumor-infiltrating lymphocytes,[21] Crohn-like lymphoid reaction,[23] and fibrotic cancer stroma[24]), have been reported in colorectal cancer. However, there are few parameters that can be used to select a patient group with a worse prognosis than that of patients with aggressive EX. With respect to the number of positive lymph nodes, eg, which is one of the most reliable prognosticators, patients with 9 or more positive nodes (only 1.5% of patients in the present cohort) had a 5-year survival rate of no less than 38.9%. Many investigators have noted that venous invasion and neural invasion observed in the primary tumor are prognostic indicators.[25-31] However, it is obvious that the prognostic impact of venous and neural invasion identified in the actively invasive frontal region of EX is much higher than that of these histologic features observed in the primary lesion.

In addition, the diameter of EX has a more important role in the estimation of postoperative survival than the contour of EX. The existence of EX of 10 mm or larger might have a prognostic impact similar to that of aggressive EX; in the present study, EX of 10 mm or larger was found in 5.7% of patients who had undergone curative resection of colorectal cancer and related to an unfavorable 5-year survival rate of 37.8%. The value of aggressive EX and EX of 10 mm or larger as prognostic indicators is comparable to that of resectable metastasis in the liver or lung; 5-year survival rates of 25% to 50% have been reported for patients undergoing potentially curative surgery for liver metastasis[32-34] and lung metastasis.[35,36] Further studies focusing on EX are necessary to identify patients at the highest risk who would be the most suitable for intensive adjuvant chemotherapy and surveillance strategies.

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ORIGINAL ARTICLE

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Polyethylene glycol solution (PEG) plus contrast medium vs PEG alone preparation for CT colonography and conventional colonoscopy in preoperative colorectal cancer staging

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Abstract *Purpose:* This study evaluated the usefulness of combined polyethylene glycol solution plus contrast medium bowel preparation (PEG-C preparation) followed by dual-contrast computed tomography enema (DCCTE) and conventional colonoscopy. The main purpose of these examinations is the preoperative staging of already known tumors. *Materials and methods:* One hundred patients with colorectal tumors were alternately allocated to either a polyethylene glycol solution preparation (PEG preparation) group (n=50) or a PEG-C preparation group (n=50) before undergoing conventional colonoscopy and computed tomographic (CT) colonography. After conventional colonoscopy, multidetector row CT scans were performed. Air images were reconstructed for both groups; contrast medium images were additionally reconstructed for the PEG-C preparation group. DCCTE images were a composite of air images and contrast medium images without use of dedicated electronic cleansing software. Quality scores (the presence or absence of blind spots of the colon) were compared between the two groups. *Results:* Complete tumor images were obtained by DCCTE for all 50 (100%) lesions in the PEG-C preparation group, as compared with only nine of the 50 lesions (18%) in the PEG preparation group (air-contrast CT enema). The overall quality score in the PEG-C preparation group was significantly better than that in the PEG preparation group (P<0.0001). *Conclusions:* DCCTE showed the entire colon without blind spots in nearly all patients in the PEG-C preparation group because the areas under residual fluid were reconstructed as contrast medium images. DCCTE and conventional colonoscopy after PEG-C preparation are feasible and safe procedures that can be used for preoperative evaluation in patients with colorectal cancer.

Keywords Colorectal neoplasms · Bowel preparation · Computed tomography · Colonography · Virtual colonoscopy

Introduction

Computed tomographic (CT) colonography have recently become a popular clinical examination tool with significant improvements being made on the quality of the images due to a rapid progress in computer technology. CT colonography is a minimally invasive examination [1–7] but residual fluid and feces in the large intestine may negatively affect diagnostic accuracy. Standard colonic cleansing leaves residual fluid and feces. This makes differential diagnosis or preoperative staging of colorectal tumors difficult. With the administration of small amounts of oral contrast medium, residual fluid and feces become identifiable [8]. Most previous investigations used fecal tagging as a bowel preparation before CT colonography for screening of colorectal tumor [2, 8–11]. These methods

also require dietary restriction during bowel preparation for 1 to 3 days.

To cope with the problem of residual fluid and feces in the large intestine, we recently developed a technique for bowel preparation that combines polyethylene glycol solution plus contrast medium preparation (PEG-C preparation) and reconstructed CT colonography images without the use of dedicated electronic cleansing software. We refer to this technique as dual-contrast CT enema (DCCTE). We previously reported that CT colonography (air-contrast CT enema) images were useful for the preoperative staging of colorectal cancer [12, 13]. Our efforts have been focused on finding a technique that could serve for the improvement of CT colonography images. PEG-C preparation without dietary restriction could possibly be used not only for CT colonography but also for conventional colonoscopy in patients undergoing preoperative assessment of colorectal cancer.

This study had two objectives. The first was to determine whether PEG-C preparation can be safely used for conventional colonoscopy, CT colonography, and surgical operation. The second was to evaluate whether CT colonography images produced by DCCTE were superior to images obtained by air-contrast CT enema after polyethylene glycol solution preparation (PEG preparation).

Table 1 Patient's characteristics

	PEG (n=50)	PEG-C (n=50)	P value
Age, years±SD	68.0 ± 10.4	64.5 ± 11.4	0.114[a] (NS)
Gender, W/M	22/28	20/30	0.839[b] (NS)
Tumor site			0.219[b] (NS)
Cecum/ascending colon	10	6	
Transverse colon	4	2	
Descending colon	1	0	
Sigmoid colon	9	18	
Rectum	26	24	
Depth of invasion (T)			0.111[b] (NS)
pTis	5	1	
pT1	6	12	
pT2	13	8	
pT3	26	29	
Dukes			0.713 [b] (NS)
A	19	17	
B	13	11	
C	18	22	
Surgical approach			0.412 [b] (NS)
Laparoscopy	28	33	
Open	22	17	

SD Standard deviation, *NS* not significant
[a]Mann–Whitney *U* test
[b]Chi-squared test

Materials and methods

Patients

Between November 2002 and October 2004, a total of 100 patients with colorectal tumor (42 women and 58 men, age range 41–88 years, mean age±SD 66.3±11.0 years) were enrolled. These patients were referred to our institution for preoperative evaluation and treatment of colorectal tumor. All patients were examined by conventional colonoscopy and CT colonography and were not in need of screening of the colon and rectum. The purposes of conventional colonoscopy were pathological diagnosis and endoscopic marking with clips or India ink for (laparoscopic) surgery. The purposes of CT colonography were precise anatomical localization of lesions and preoperative comprehensive staging, with depth of cancer invasion, regional and distant lymphadenopathies, and metastases [12].

Patients were alternately allocated to either a PEG preparation group (n=50) or a PEG-C preparation group (n=50) before preoperatively undergoing conventional colonoscopy and CT colonography. The clinical characteristics of the two groups are shown in Table 1. Patients with acute bowel obstruction were excluded.

Before bowel preparation, two experienced gastroenterologists (K. N. and S. E.) provided all patients with a detailed description of the scheduled procedures and possible complications, such as discomfort, radiation exposure, and urge to defecate. Written informed consent was obtained from each patient before enrolment.

Safety analysis

The osmotic pressure of PEG-C solution and the metabolism of PEG-C solution by colonic bacteria were examined to confirm the safety of the solution. The osmotic pressure of PEG-C solution and the osmolarity (PEG-C solution to physiological saline ratio) was measured six times with a freezing point depression osmometer (OM802, Vogel, Germany). Hydrogen concentrations were determined by gas chromatography using a molecular sieve column and reduction detector (GC-8A, Shimadzu, Japan).

Bowel preparation

Diet was unrestricted to either group until the day before the procedures. On the day of the examination, no breakfast was allowed, and both bowel preparations were performed between 8:00 and 10:00 A.M.

PEG preparation group On the day of the examination, patients were given 2 l of polyethylene glycol solution (Niflec; Ajinomoto Pharma, Tokyo, Japan) over the course of 2 h as standard colonoscopic cleansing.

PEG-C preparation group On the day of the examination, patients were given 1,620 ml of PEG solution over the course of 2 h, followed by 400 ml of PEG-C solution, consisting of 380 ml of PEG solution plus 20 ml of water-soluble contrast medium (Gastrografin, amidotrizoic acid and diatrizoic acid, Nihon Schering, Osaka, Japan). We used water-soluble contrast medium for residual fluid tagging purposes.

Examination techniques

After PEG or PEG-C preparation, all patients underwent conventional colonoscopy. The endoscopists were blinded to the assigned preparation. When necessary, the intestinal lumen was endoscopically marked with clips or India ink to localize tumors precisely during laparoscopic or open colorectal operations. The main tumor was clinically staged by evaluating its morphologic characteristics on the application of sprayed dye, endoscopic ultrasonographic features, and pit pattern [14], assessed with the use of a magnifying colonoscope (CF-Q240ZL/I, Olympus, Tokyo, Japan). Any colonic tumors apart from the main tumor underwent endoscopic polypectomy or endoscopic mucosal resection without reservation.

After conventional colonoscopy, multidetector-row CT (MDCT) scans were obtained on the same day. The patient's large intestine was inflated gently with room air. Immediately before MDCT scanning, a smooth muscle relaxant, 20 mg of scopolamine butylbromide (Buscopan, Nippon Boehringer Ingelheim, Kawanishi, Japan) or 1 mg of glucagon (Glucagon G Novo, Eisai, Tokyo, Japan), was given intravenously. The adequacy of colonic distention was assessed on the anteroposterior scout image. If the colon was adequately distended, MDCT scanning was performed. If not, additional air was insufflated.

Eight-detector row CT scans were performed with an Aquilion M8 CT scanner (Toshiba, Tokyo, Japan). The patients underwent single scans in a single position; dual positioning was not used. One hundred milliliters of nonionic iodinated contrast material (Iopamiron 300, iopamidol, Nihon Schering, Osaka, Japan or Omnipaque 300, iohexol, Daiichi Pharma, Tokyo, Japan) was injected intravenously with a 90-s delay time and an infusion rate of 2 ml/s to evaluate the presence of metastases or invasion. The entire region of the abdomen and pelvis was scanned in a single run. CT images were acquired at 120 kVp and 250 mAs with the use of 8×2-mm collimation, a pitch of 7.0–13.0, and a 1-mm reconstruction interval. Air-contrast images were reconstructed for both groups; contrast medium images were additionally reconstructed for the PEG-C preparation group. The DCCTE images were a composite of air images and contrast medium images (Fig. 1). We did not remove residual fluid electrically with dedicated electronic cleansing software. Virtual three-dimensional endoscopic display, i.e., virtual colonoscopy, was not assessed in this study.

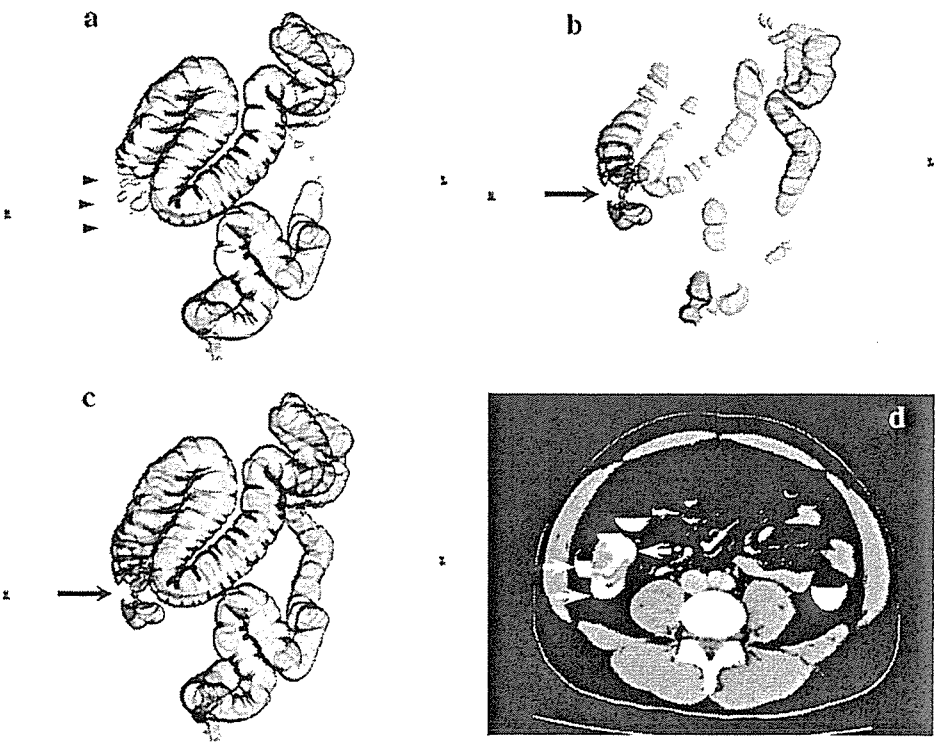

Fig. 1 Dual-contrast CT enema in PEG-C preparation group: **a** Air image (air-contrast CT enema) shows blind spots in the cecum and proximal descending colon. Air images cannot detect the lesion because it is concealed by residual fluid in the cecum (*arrowheads*). **b** Contrast-medium image can detect a severe deformity in the cecum (*arrow*). **c** Dual-contrast CT enema is a composite figure of the air image and contrast medium image. Dual-contrast CT enema clearly demonstrates severe deformity (so-called apple-core-like deformity) (*arrow*) and the course and length of the entire large intestine, without blind spots. **d** In transverse two-dimensional CT image, residual fluid is homogeneously tagged throughout the cecum (*arrow*)

Image analysis

Conventional transverse CT colonographic images were used for the detection of extracolonic abnormalities or metastases and for preoperative staging. Using the data obtained by MDCT, we reconstructed CT colonography (air-contrast CT enema and DCCTE) images with the use of a ZIO M900 workstation (Zio Software, Tokyo, Japan). Air-contrast CT enema images after PEG preparation and DCCTE images after PEG-C preparation were assessed with regard to the ability to detect tumor, tumor localization, and the presence or absence of blind spots of the large intestine. Blind spots are defined as the spots of the large intestine which cannot be reconstructed by air images or contrast medium images. Although endoscopic marking with metal clips was recognizable in conventional transverse CT images, clips were not used for detecting tumor in image analysis. Tumor location at surgery was regarded as the gold standard against the results of air-contrast CT enema and DCCTE. The imaging quality of CT colonography (the presence or absence of blind spots) was scored according to a five-point scale (5, excellent—no blind spots; 4, good—blind spot area only 25%; 3, fair—blind spot area 50%; 2, poor—blind spot area 75%; and 1, very poor—a given segment of the colon was completely blinded by residual fluid). This analysis was performed for five segments of the colon (1, cecum/ascending colon; 2, transverse colon; 3, descending colon; 4, sigmoid colon; and 5, rectum) by scrolling through the CT colonography images (air-contrast CT enema and DCCTE). Two readers [a gastroenterologist (K. N.) and a radiologist (T. I.)] separately and independently interpreted the air-contrast CT enema images and DCCTE images. Additional colorectal polyps missed by conventional colonoscopy were not assessed.

The Hounsfield units (HU) values for residual fluid in the cecum/ascending colon and the rectum were measured for all patients in the PEG and PEG-C preparation groups. The HU values were measured by manually circling regions of interest. The mean HU values for residual fluid were calculated.

Statistical analysis

The statistical significance of differences in patients' characteristics was assessed with the use of the Mann–Whitney *U* test and chi-squared test. The Mann–Whitney *U* test was used to compare differences in quality scores between the PEG preparation group and PEG-C preparation group according to segment, differences in inter-reader quality scores, differences in HU values of residual fluid between the PEG preparation group and PEG-C preparation group, and differences in HU values of residual fluid between the cecum/ascending colon and the rectum. Differences with *P* values of less than 0.05 were considered statistically significant.

Results

The osmotic pressure of PEG-C solution was 384±3.3 mOsm/l (mean±SD). The ratio of PEG-C solution osmolarity to physiological saline osmolarity was 1.337±0.012. The fecal suspensions generated only 824 to 845 ppm hydrogen, an explosive gas, when incubated with PEG-C solution for 2 h (Table 2). This corresponds to 1/50 of the minimum explosive concentration of hydrogen (> 40,000 ppm) [15].

The PEG and PEG-C preparations were completed safely and successfully in all 100 patients. No side effects (vomiting, bowel obstruction, or bowel perforation) were associated with bowel preparation.

After PEG or PEG-C preparation, conventional colonoscopy was preoperatively performed in all 100 patients. The quality of bowel preparation was satisfactory in all patients for conventional colonoscopy. Colonoscopic examination and treatment were successfully performed after PEG-C preparation, with no problem in any patient. To localize tumors during surgery, endoscopic marking with clips was used for 37 of the 50 cases in the PEG preparation group and 35 of the 50 cases in the PEG-C preparation group. The differences in frequency of clip usage were not statistically significant. Preoperative staging by conventional transverse CT colonographic images using MDCT data was performed in all 100 patients without any problem.

In the PEG preparation group, the detection rate of tumor on air-contrast CT enema was 96% (48 of the 50 lesions). One slightly elevated (pTis) lesion and 1 ulcerated (pT2) lesion were not detected (Fig. 2) because of residual fluid. Complete tumor images were obtained by air-contrast CT enema for only nine of the 50 lesions (18%). In the PEG-C preparation group, complete tumor images were obtained by DCCTE for all 50 lesions (100%). Even when tumors were hidden by residual fluid in the colon, the DCCTE successfully detected all tumors not detected on air-contrast CT enema (Fig. 1). The DCCTE showed regions of the large intestine that would have been concealed by residual fluid after PEG preparation (Fig. 1). Accurate tumor

Table 2 Hydrogen concentrations (ppm) after incubation of PEG-C solution with human feces

No. of trials	Time of incubation (h)				
	0	2[a]	4	6	8
1	<500	824	1,269	1,412	1,306
2	<500	845	1,353	1,526	1,445

Minimum explosive concentration for hydrogen > 40,000 ppm
ppm Parts per million
[a]Time of the PEG-C preparation ≤2 h

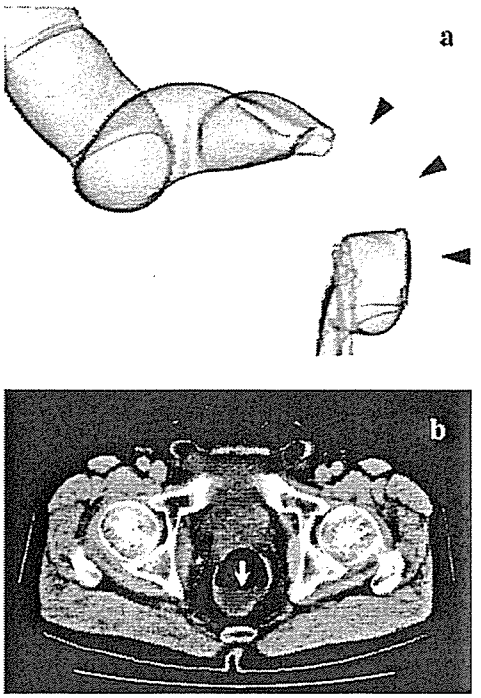

Fig. 2 Air-contrast CT enema in PEG preparation group: **a** Air-contrast CT enema shows a blind spot in the rectum. The ulcerated lesion (*pT2*) in the rectum was not detected (*arrowheads*). **b** In the transverse two-dimensional CT image, the tumor was concealed by residual fluid in the rectum (*arrow*).

localization by air-contrast CT enema and DCCTE were 96 and 100%, respectively.

Tables 3 and 4 show the quality of images obtained by CT colonography after PEG preparation and PEG-C preparation, respectively. With PEG preparation, the average image quality scores per segment ranged from 4.34±0.92 (transverse colon) to 2.34±1.29 (rectum) for reader 1 and from 4.54±0.58 (transverse colon) to 2.62±1.24 (rectum) for reader 2 (Table 5). With PEG-C preparation, the average image quality scores per segment ranged from 5.0±0.0 (cecum/ascending colon) to 4.86±0.45 (rectum) for reader 1 and from 5.0±0.0 (descending colon) to 4.92±0.27 (sigmoid colon and rectum) for reader 2 (Table 5). The DCCTE demonstrated nearly all areas of the colon and rectum, without blind spots. There were clear differences between PEG preparation and PEG-C preparation in all segments. The inter-reader differences in quality scores were not statistically significant (Table 6).

Table 7 shows the HU values of residual fluid in the cecum/ascending colon and the rectum for the PEG and PEG-C preparation groups. In the PEG preparation group, the HU values of residual fluid were 65 HU or less. In the PEG-C preparation group, the HU values of residual fluid were 130 HU or higher, and the mean HU value was 433 HU in the cecum/ascending colon and 329 HU in the rectum.

Discussion

An accurate preoperative staging for colorectal cancer is essential for a correct therapeutic plan, including surgery (limited or extensive resection), radiotherapy, or chemotherapy (advanced stage disease). the increased popularity of laparoscopic surgery for the treatment of colorectal cancer has heightened the importance of preoperative diagnosis. Accurate tumor localization is imperative because the colon and rectum cannot be palpated laparoscopically. A survey of the members of the American Society of Colon and Rectal Surgeons reported that 18 of 278 respondents (6.5%) had previously chosen the wrong segment of the colon for laparoscopic colectomy, requiring conversion to standard laparotomy and an additional resection [16].

An accurate preoperative diagnosis is also important because laparoscopic approaches to colorectal tumor, including factors such as port positions, incision site and size, and extent of resection, are based on lesion size and location. Although the conventional colonoscopy has high diagnostic accuracy for colorectal tumor, the error rate for preoperative tumor localization ranges from 14 to 22% [12, 17]. By contrast, CT enema can precisely define the

Table 3 Distribution of quality scores with PEG preparation (air-contrast CT enema)

	Quality scores (presence or absence of blind spots of the large intestine)				
	1 (reader 1/reader 2)	2 (reader 1/reader 2)	3 (reader 1/reader 2)	4 (reader 1/Reader 2)	5 (reader 1/reader 2)
Cecum/ascending colon	3/2	8/6	15/6	19/29	5/7
Transverse colon	1/0	1/0	6/2	14/19	28/29
Descending colon	14/10	12/10	14/14	9/12	1/4
Sigmoid colon	1/1	4/4	5/4	9/17	31/24
Rectum	17/8	13/22	10/6	6/9	4/5
Total	36/21	38/42	50/32	57/86	69/69
Percentage	(14.4/8.4)	(15.2/16.8)	(20.0/12.8)	(22.8/34.4)	(27.6/27.6)

Quality scores: 5, excellent—no blind spots; 4, good—blind spot area only 25%; 3, fair—blind spot area 50%; 2, poor—blind spot area 75%; and 1, very poor—a given segment of the colon was completely blinded by residual fluid

Table 4 Distribution of quality scores with PEG-C preparation (dual-contrast CT enema)

	Quality scores (presence or absence of blind spots of the large intestine)				
	1 (reader 1/reader 2)	2 (reader 1/reader 2)	3 (reader 1/reader 2)	4 (reader 1/reader 2)	5 (reader 1/reader 2)
Cecum/ascending colon	0/0	0/0	0/0	0/1	50/49
Transverse colon	0/0	0/0	0/0	1/1	49/49
Descending colon	0/0	0/0	0/0	2/0	48/50
Sigmoid colon	0/0	0/0	1/0	0/4	49/46
Rectum	0/0	0/0	2/0	3/4	45/46
Total	0/0	0/0	3/0	6/10	241/240
Percentage	(0/0)	(0/0)	(1.2/0)	(2.4/4.0)	(96.4/96.0)

Quality scores: 5, excellent—no blind spots; 4, good—blind spot area only 25%; 3, fair—blind spot area 50%; 2, poor—blind spot area 75%; and 1, very poor—a given segment of the colon was completely blinded by residual fluid

anatomical locations of lesions. We previously reported that accurate tumor localization by air-contrast CT enema was 97.3% [12]. This study shows that DCCTE is expected to enhance the accuracy of tumor localization because the imaging of complete tumor is superior to that on air-contrast CT enema.

An accurate assessment of the course and length of the large intestine also plays a key role in deciding the optimal approach for laparoscopic treatment as well as the type of anastomosis, extent of resection, and stoma site. The DCCTE delineated the course and length of nearly the entire large intestine without blind spots because the areas under residual fluid were reconstructed as contrast medium images. One of the major advantages of PEG-C preparation is the induced difference in HU values between the residual fluid and the colonic wall. Callstrom et al. [8] used a threshold value of 150 HU for the electronic removal of well-tagged stool. With PEG-C preparation, the contrast medium was diluted by residual fluid, but nearly all HU values of residual fluid in the colon remained higher than 150 HU. The values were high enough to differentiate the residual fluid from the colonic wall and tumors (Table 7). The variability of the HU values of residual fluid in the PEG-C group was relatively low (Table 7).

For well-tagged residual fluid, enough amounts of contrast media are needed. Fewer amounts of contrast media are preferred for patient acceptability because water-soluble contrast medium tastes bitter. We used only 20 ml of water-soluble contrast medium in PEG-C preparation. In the PEG-C preparation group, the HU values of residual fluid were *high* enough to reconstruct good contrast medium images (Table 7). PEG-C preparation is also safe for conventional colonoscopy, CT colonography, and surgery. Intracolonic explosions are rare complications of electrocautery during endoscopic treatment or surgery. These explosions result from the ignition of hydrogen or methane, two products of colonic bacterial fermentation. The PEG-C solution is virtually unfermented by colonic bacteria. The PEG-C preparation is, therefore, useful in cleansing the large intestine of patients who undergo CT colonography as well as conventional colonoscopy before surgery for colorectal tumor. In addition, the PEG-C preparation does not require any dietary restrictions. However, the administration of 2 l of PEG with PEG-C solution is of less volume than that of European standard bowel preparation and it warrants further examination.

The DCCTE does not require removal of residual fluid from the large intestine before examination and can be performed before conventional colonoscopy. However, conventional colonoscopy procedures immediately after CT colonography are technically difficult even for experienced colonoscopists owing to the presence of air in the colon [12]. Such air makes examinations time-consuming and uncomfortable for patients. MDCT scans are, therefore, performed after conventional colonoscopic examination at our hospital.

In addition to the creation of CT colonography images, preoperative MDCT data can be used for the detection of extracolonic abnormalities or metastases and for clinical staging in patients with colorectal cancer [18–20]. Because patients with colorectal cancer usually undergo preoperative staging by abdominal and pelvic CT and conventional

Table 5 Mean quality scores of CT colonography (presence or absence of blind spots)

	Cecum/ascending colon		Transverse colon		Descending colon		Sigmoid colon		Rectum	
	PEG	PEG-C	PEG	PEG-C	PEG	PEG-C	PEG	PEG-C	PEG	PEG-C
Reader 1	3.30	5.00	4.34	4.98	2.42	4.96	4.30	4.96	2.34	4.86
	$P< 0.0001$		$P< 0.0001$		$P< 0.0001$		$P< 0.0001$		$P< 0.0001$	
Reader 2	3.66	4.98	4.54	4.98	2.80	5.00	4.18	4.92	2.62	4.92
	$P< 0.0001$		$P< 0.0001$		$P< 0.0001$		$P< 0.0001$		$P< 0.0001$	