and Grade 0 in 1 patient. In addition, using the MAT method, the same patients each showed a score of 6 points or higher.

Subsequently, the medication was switched from granisetron to palonosetron as a second-line antiemetic. The CTCAE 4.0 classification of nausea/vomiting decreased to Grade 1 or less in all 8 patients, while the MAT method showed that nausea/vomiting was completely suppressed to a score of 0 points in 3 patients and to a score of 4 points or less in the remaining 5 patients. None of the 8 patients expressed a desire for another antiemetic. There were no serious antiemetic-related adverse effects that were considered to have been caused by palonosetron (Table 2).

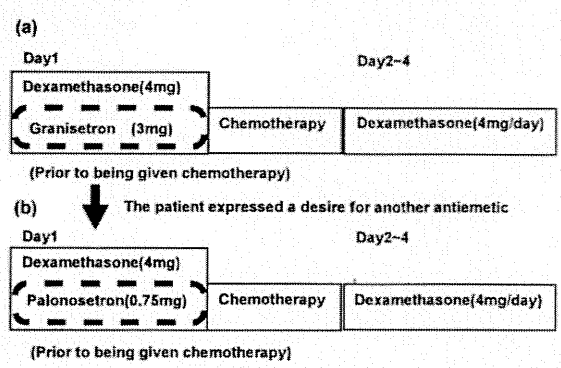

Figure 1: a) Prior to being given chemotherapy, the patients were given granisetron (0.75 mg, intravenous) and dexamethasone (4 mg, intravenous) as first-line antiemetics. On days 2-4 after starting the chemotherapy, dexamethasone (4 mg) was administered orally. b) When the patients expressed a desire for another antiemetic, the medication was switched from granisetron to palonosetron as a second-line antiemetic.

	Granisetron			Palonosetron	
Age	Sex (grade)*	Nausea/vomit score	**MAT (grade)*	Nausea/vomit score	**MAT
57	M	(G2)/(G1)	7	(G0)/(G0)	1
61	M	(G2)/(G1)	6	(G1)/(G0)	0
49	M	(G2)/(G0)	8	(G1)/(G0)	0
51	F	(G2)/(G2)	8	(G1)/(G0)	3
56	M	(G2)/(G2)	10	(G1)/(G0)	4
54	F	(G2)/(G1)	8	(G1)/(G0)	4
69	M	(G2)/(G1)	9	(G0)/(G0)	0
52	F	(G2)/(G2)	7	(G1)/(G0)	1

*CTCAE 4.0 grade
**Maximum: acute and delayed CIMV

Table 1: The results of eight patients expressed a desire for another antiemetic (Forty-two patients did not expresse a desire for another antiemetic).

	Grade 1-2	Grade 3-4
Constipation	0 (0%)	0 (0%)
Headache	0 (0%)	0 (0%)
Increased AST concentration	0 (0%)	0 (0%)
Prolonged ECG QTc	0 (0%)	0 (0%)
Increased ALT concentration	0 (0%)	0 (0%)
Angiopathy	0 (0%)	0 (0%)
Protein urine present	0 (0%)	0 (0%)
Increased blood bilirubin concentration	0 (0%)	0 (0%)
Increased ganma-GTP concentration	0 (0%)	0 (0%)
Constipation	0 (0%)	0 (0%)

Table 2: Toxicity (CTCAE v4.0).

Discussion

The efficacy rates of the mainstay FOLFOX chemotherapy regimen, which consist of combinations of 5-fluorouracil, Oxaliplatin, and leucovorin, in the treatment of unresectable, advanced, recurrent colorectal cancer are generally said to be in the range of about 50-60% [9,10]. Moreover, in recent years, molecularly targeted drugs such as bevacizumab, cetuximab, and panitumumab have been added to the therapeutic arsenal, and the survival rate has been prolonged [3,4,11-13]. However, chemotherapy-related adverse reactions have become an issue, and, in particular, it is said that 70-80% of patients undergoing CINV [14]. Moreover, the patients themselves rank CINV as top issues causing misgivings regarding their cancer chemotherapy [5,6]. In addition, CINV can not only exert bad effects, such as anorexia and malnutrition, but it can also lead to a marked decrease in the patient's QOL and interfere with continuation of the cancer chemotherapy.

In consideration of that situation, the National Comprehensive Cancer Network (NCCN) and American Society for Clinical Oncology (ASCO) have prepared guidelines for antiemetic therapy. In these guidelines, the FOLFOX regimens for unresectable, advanced, recurrent colorectal cancer are classified as Moderate Emetic Risk (MER) in the emesis risk classification. In Japan, many institutions administer granisetron and dexamethasone as first-line antiemetics. However, it is said that these agents are unable to control CINV in some patients. Nevertheless, to date, there have been few reports of studies aimed at identifying effective antiemetics for colorectal cancer patients. The objective of the present study was to generate data in regard to this important aspect of patient care.

Our findings indicated that 84% of patients did not express a desire for another antiemetic, but 16% of patients expressed a desire for it. Control of CINV was poor in 16% of colorectal cancer patients undergoing chemotherapy and that a back-up strategy was needed for management of CINV in such cases. Palonosetron, the second-generation 5-HT3 receptor antagonist that was used in this study, is characterized by stronger affinity for the 5-HT3 receptor and a plasma half-life that is 40 hours longer in comparison with granisetron, which is a first-generation antiemetic [7]. Prior to this, Saito et al. performed a comparative study of palonosetron and granisetron as first-line antiemetics for acute and delayed CINV caused by high-emetic-risk chemotherapy in breast cancer patients. They reported that palonosetron was significantly more effective than granisetron in suppressing CINV [15].

The present study focused on 50 patients who received the FOLFOX regimen, which are classified as MEC in the emesis risk classification, to treat unresectable, advanced, recurrent colorectal cancer. CINV for 8 patients was not effectively controlled by granisetron and dexamethasone as first-line antiemetics. However, when palonosetron was given as a second-line antiemetic, replacing granisetron, it was found to safely control CINV in all patients.

Granisetron/palonosetron can be thought to have improved the patients' QOL, relieved their anxiety, and contributed to continuation of the chemotherapy.

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症例報告

HIPECを含む集学的治療により長期生存が得られた腹膜播種（P3）を伴う横行結腸癌の1例

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内容要旨

57歳女性．腹膜播種（P3）と左卵巣転移を伴う横行結腸癌に対し，拡大右半結腸切除，D3郭清，腹膜播種切除（臍部，ダグラス窩，大網），両側卵巣切除，術中温熱化学療法（以下HIPEC）を施行した．最終診断はT，2型，80×35mm，pSE，pN2，sH0，sP3，cM0，fStage Ⅳであった．術後は化学療法（mFOLFOX6半年間，以後1-LV/5FU）を施行した．初回手術から1年3カ月後のCT検査において左右横隔膜下や脾臓周囲などに腹膜再発が出現し，腹膜播種切除（正中創瘢痕部，肝表面，胃前後壁，小網，脾摘，左右横隔膜部分切除），HIPECを施行した．術後は化学療法（mFOLFOX6）を施行した．初回手術から4年後に肝S6に20mm大の転移病変と，肝門部に孤立性リンパ節腫大を認め，肝部分切除，リンパ節郭清を施行したが術中所見では腹膜播種の再発は認められなかった．

本例は広範囲に腹膜播種が認められながらも積極的な切除とHIPECおよびmFOLFOX6が有効に働き，腹膜播種のコントロールがなされ長期生存が得られた症例と考えられた．

索引用語：結腸癌，腹膜播種，HIPEC

はじめに

一般に消化器癌の腹膜播種症例は予後不良であることが多く，外科的切除の適応外となることが多いが[1)~4)]，われわれは適応症例を選んだ上で播種巣を切除し術中温熱化学療法（hyperthermic intraperitoneal chemotherapy：以下HIPEC）を導入し予後の改善を得ることができた症例を報告してきた[5)6)]．また近年，化学療法もFOLFOX，FOLFIRI療法や分子標的薬などの新規治療が開発され予後の改善がみられている．

今回われわれは横行結腸癌腹膜播種（P3）に対し，2度の腹膜播種切除とHIPECおよび術後化学療法を施行し有効な効果が得られた症例を経験したので報告する．

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連絡先　中澤俊之
〒910-1193　福井県吉田郡永平寺町松岡下合月23-3
福井大学第一外科

症　例

患　者：57歳，女性．

主　訴：貧血．

既往歴：40歳，子宮筋腫にて子宮全摘術，慢性関節リウマチ．

家族歴：特記すべきことなし．

現病歴：貧血を指摘され精査目的に紹介となる．

入院時現症：身長149.2cm　体重31.4kg　2年間で10kgの体重減少あり．

眼瞼結膜：貧血あり，黄疸なし，腹部平坦軟，圧痛なし，下腹部正中に手術痕あり，右肋弓下に可動性不良な硬い腫瘤を触知．

血液検査所見：RBC418万/mm^3，Hb9.0g/dlと貧血を認めた．電解質，肝機能，腎機能に異常所見は認められなかった．腫瘍マーカーはCEA

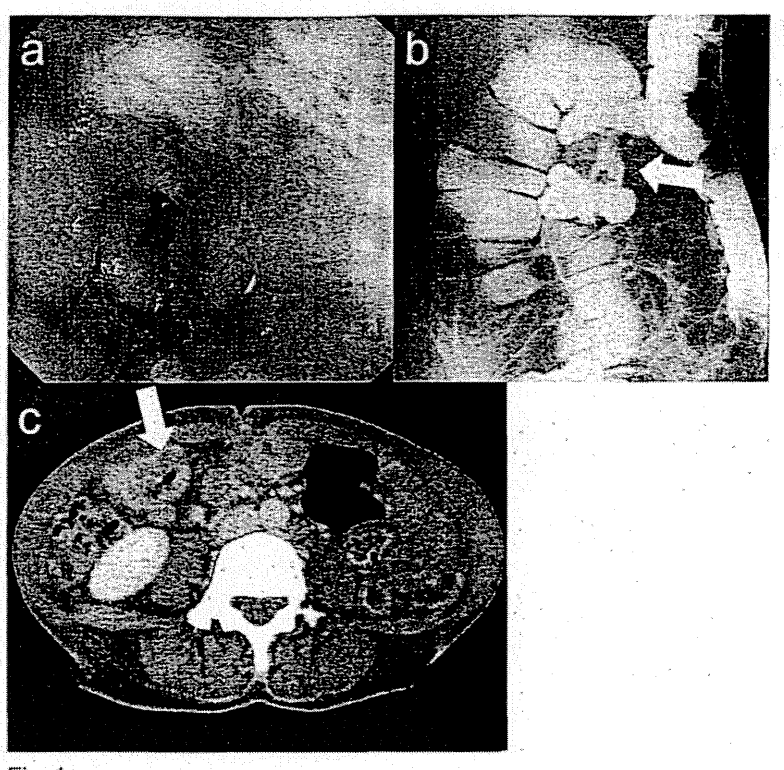

Fig. 1
(a) Colonoscopy examination showed type2 transverse colon cancer.
(b) Contrast enema showed stenosis at the transverse colon (arrowhead).
(c) Enhanced CT scan of the abdomen showed a tumor of the transverse colon whose edge was enhanced.

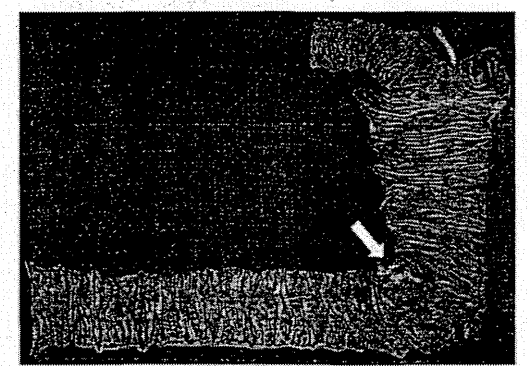

Fig. 2 Resected specimen showed type2 tumor in the transverse colon.

10.3ng/mlと上昇していた.

下部消化管内視鏡検査：横行結腸右側に全周性の2型病変を認め，腫瘍による狭窄で内視鏡の通過は不能であった（**Fig. 1a**）．生検よりGroup V（tub2）と診断した.

注腸造影：横行結腸右側に全周性の高度狭窄を認めた（**Fig. 1b**）.

腹部CT検査：横行結腸に辺縁の造影効果を伴う全周性の壁肥厚を認めた（**Fig. 1c**）．また横行結腸間膜内にリンパ節の腫脹を認めた.

リゾビストMRI：肝転移を疑う陰影は認めなかった.

術前診断：T，2型，cSE，cN1，cH0，cP0，cM0，cStage Ⅲa（取扱規約第7版補訂版）[7]と診断し手術を施行した.

手術所見：原発巣は横行結腸右側にあり，また大網，臍部腹膜，ダグラス窩，左卵巣に腹膜転移を認めた．術式は拡大右半結腸切除，D3郭清，腹膜播種切除（臍部，ダグラス窩，大網），両側卵巣切除（右側卵巣は予防的に切除）の後，HIPEC［シスプラチン（以下CDDP）150mg，マイトマイシンC（以下MMC）20mg，エトポシド（以下VP16）

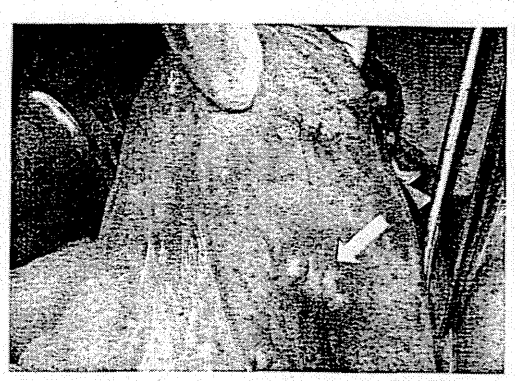

Fig. 4 Intraoperative photograph. Dissemination was found on the serosa of the stomach wall (arrowhead).

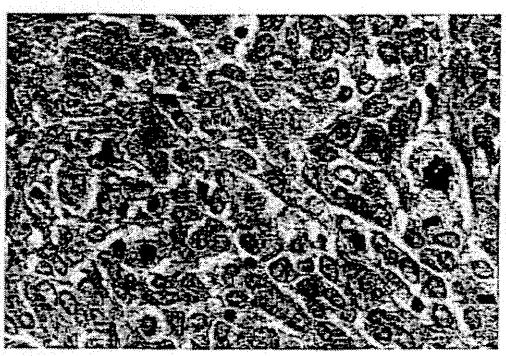

Fig. 5 Pathological finding for peritoneal dissemination showing poorly differentiated adenocarcinoma (HE, ×200).

郭清（No12）を施行した．しかし術中所見で腹膜再発は認められなかった．病理組織診断で切除した病変は中分化から低分化な腺癌で，横行結腸癌の肝転移，肝所属リンパ節転移（No12）を認めた．術後は化学療法（mFOLFOX6）を現在まで10カ月間継続しており再発なく経過している．初回手術から4年10カ月生存中である．

考　察

大腸癌研究会・大腸癌全国登録調査報告（1995～1998年）によると大腸癌同時性遠隔転移頻度は結腸癌6.4%，直腸癌3.0%にみられるとされている[8]．腹膜播種症例の治療成績は限局性の播種（P1，P2）と広範囲な播種（P3）で大きく差があり，生存期間中央値は，山口ら[1]はP1：34.6カ月，P2：22.3カ月，P3：13.3カ月，平井ら[2]はP1：17.7カ月，P2：13.8カ月，P3：6.6カ月と報告している．大腸癌治療ガイドラインでは，P1，P2で他に切除不能な遠隔転移がなく過大浸襲とならない切除であれば原発巣切除と同時に腹膜播種を切除することが望ましいと記載されているが，P3の切除効果は確立されていない[8]．

一方，海外では限られた施設ではあるが広範囲な腹膜播種に対しても全腹膜切除とHIPECの併用が行われており，完全切除が可能なものに対してはその有効性が示されている[9]～[11]．

また腹膜播種を伴う大腸癌に対する全身化学療法の有効性については画像診断による病変の評価が難しいため少ないが，最近ではFOLFOXの有効性について報告されている[12][13]．

当科では大腸癌の腹膜播種を認める症例で，腹膜転移以外の因子が根治的に切除可能でかつ75歳以下で心血管・呼吸器・腎臓の機能障害を認めない症例に対し可及的に腹膜播種切除とHIPECを施行している[5][6][14]．当科のHIPECの方法は特にThermal doseを重要と考えており，43℃，40分を標準としている[5][6]．また術後は進行大腸癌の化学療法として，mFOLFOX6あるいはFOLFIRI療法を行っている．

本症例は初回手術時に腹膜播種が広範囲にみられ，P3に分類される症例であったが[7]，腹膜播種以外が根治的に切除可能であり，原発巣，腹膜播種巣切除ならびにHIPECを施行した．術後はmFOLFOX6を半年間施行し，その期間再発所見は認めず腹膜播種はコントロールされていたと考えられた．

初回の術後1年3カ月目に，脾周囲や肝周囲，横隔膜下，胃壁表面に腹膜播種の再発を認めたが，その他に血行性転移もなく可及的に切除可能と判断し，再度腹膜播種の切除とHIPECを施行した．初回術後の治療経過から2回目の術後には再度mFOLFOX6を施行した．

また初回手術より4年経過後に肝転移と肝所属リンパ節の転移を認めたが，切除可能であり再度手術を施行した．その際，術中所見では腹腔内に明らかな腹膜播種は認めず積極的な切除とHIPECおよびmFOLFOX6療法が著効していたものと考えられた．

腹腔内は血液-腹膜関門や腹膜播種による間質

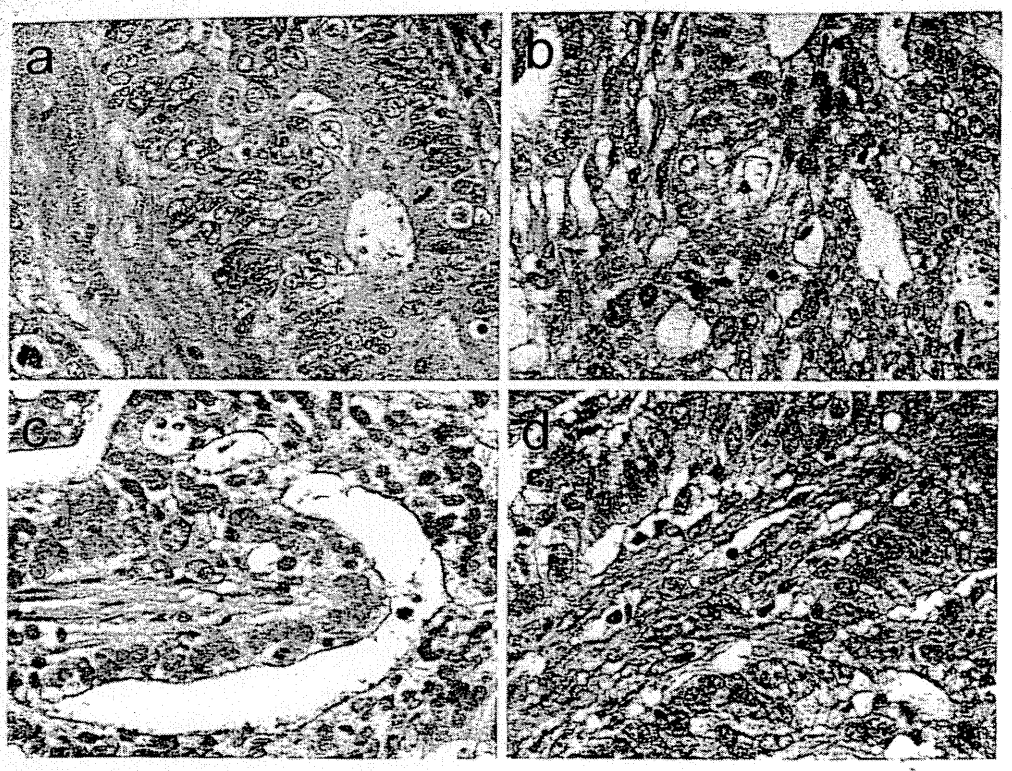

Fig. 3
(a) Pathological findings for transverse colon cancer showing tub2 (HE, ×200).
(b) Pathological findings for left ovary showing tub2 (HE, ×200).
(c) Pathological findings for navel peritoneal disseminations showing moderately to poorly differentiated adenocarcinoma (HE, ×200).
(d) Pathological findings for peritoneal disseminations at the Cul-de-sac showing moderately to poorly differentiated adenocarcinoma (HE, ×200).

200mgを4Lの温生食に溶解し，Thermal dose 40分で施行を施行した．病理組織診断では横行結腸の原発巣（**Fig. 2**）は主にtub2からなり（**Fig. 3a**），浸達度pSE，脈管浸襲ly2，v2，リンパ節転移pN2であった．その他，腹膜播種巣（臍部，ダグラス窩，大網，左卵巣）からも中分化腺癌の転移が認められた（**Fig. 3b-d**）．以上より最終診断はT，2型，80×35mm，pSE，pN2，sH0，sP3，cM0，fStage Ⅳ（取扱規約第7版補訂版）[7]とした．

術後経過：術後の化学療法としてmFOLFOX6（L-OHP 85mg/m^2，1-LV 200mg/m^2，5-FU（急速静注）400mg/m^2，5-FU（46時間持続静注）2,400mg/m^2）を半年間施行した．その後LV/5-FU（1-LV 250mg/m^2，5-FU 600mg/m^2）を施行した．初回手術から1年3カ月後のCT検査において左右横隔膜下や脾臓周囲に腹膜再発巣が出現し手術を施行した．手術所見では正中創瘢痕部，肝表面，左右横隔膜下，脾門部，小網内，胃前後壁に腹膜播種巣を認めたが（**Fig. 4**），小腸，腸間膜，ダグラス窩には明らかな腹膜播種は認めなかった．

手術は腹膜播種切除術（正中創瘢痕部，肝表面，胃前壁・後壁，小網，脾摘，左右横隔膜部分切除）ならびにHIPECを施行した．病理組織診断では切除した病変はいずれも低分化腺癌からなる腹膜播種であった（**Fig. 5**）．術後は化学療法（mFOLFOX6）を継続した．初回手術から4年後のCT検査で肝S6に20mm大の結節影と，肝門部に孤立性リンパ節腫大を認め，横行結腸癌の肝転移およびリンパ節転移と診断し肝部分切除，肝所属リンパ節

結合織の影響から，全身投与された薬剤の移行が悪い．また腹腔内の薬剤濃度を高めるために直接腹腔内へ投与された薬剤は，腹膜下の数μm～2mm程度までしか浸透しないが，HIPECでは，腹膜下への薬剤の浸透性を高め，最大3mm程度まで到達すると考えられている[15)16)]．またHIPECでは温熱により抗癌剤の細胞内移行促進効果や薬剤耐性細胞の薬剤感受性を上げる作用があると言われている[15)17)]．

一方mFOLFOX6療法についてはL-OHPの腹膜移行の報告がないため，作用機序については不明であるが，癌性腹水を伴う大腸癌症例にmFOLFOX6療法が著効し癌性腹水が消失したとの報告[18)]や，癌性腹膜炎による腸閉塞の改善がみられたとの報告[19)]があり今後，作用機序や有効性についての更なる検討が必要と考えられる．

本症例の治療が著効した理由としては，初回手術や再手術時に認められた腹膜播巣のなかで肉眼的に確認できる結節性のものは可及的に切除し，ミクロレベルの微小なものについては，2度のHIPECとmFOLFOX6療法によりコントロールできたためと考えられた．

本例は，横行結腸癌と広範囲の腹膜播種（P3）に対してHIPECを含む集学的治療が有効に働き長期生存が得られた貴重な症例であると考えられたため報告した．

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A Long Survived Case of Transverse Colon Cancer with Peritoneal Dissemination Treated by Multidisciplinary Treatment Including Hyperthermic Intraperitoneal Chemotherapy

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A 57-year-old woman underwent extended right hemicolectomy, bilateral oophorectomy, resection of peritoneal disseminations and HIPEC for transverse colon cancer with disseminations. She received chemotherapy with mFOLFOX6 and l-LV/5FU after operation. About 1 year after the first operation, dissemination on the peritoneum was detected by CT. She underwent resection of peritoneal disseminations and HIPEC again. She was followed by chemotherapy with mFOLFOX6. About 4 years after the first operation, liver metastasis and hilar lymphatic metastasis were detected by CT. The resection of liver metastasis and lymphatic metastasis were performed, revealing that no dissemination was present in the peritoneal cavity. We recognized HIPEC and mFOLFOX6 were effective to her.

This case suggests that HIPEC and mFOLFOX6 are effective for the widely disseminations and she survived for long term.

Key words: colon cancer, peritoneal disseminations, HIPEC

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症　例

術前化学療法で5年生存した大動脈周囲リンパ節転移胃癌の1例

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木村俊久[1]　田畑信輔[1]　戸川　保[1]
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症例は68歳の男性で，腹部大動脈周囲リンパ節に高度の転移を認める3型低分化腺癌に対して術前化学療法を施行した．内容はPaclitaxel 60mg/body，Cisplatin 25mg/bodyをday1，day8，day15に投与しday22は休薬，同時にS-1 100mg/bodyをday1より3週投与し，1週休薬とした．以上を1コースとして計4コースを施行した．術前化学療法終了1カ月後に幽門側胃切除（D2＋No.16b1リンパ節，No.16a2リンパ節郭清），左副腎合併切除を施行した．病理組織学的検索では，主病巣，リンパ節ともに癌細胞を認めずComplete Response Grade3と判定した．その後S-1 80mgを2年間投与し，術後5年間再発を認めていない．

索引用語：術前化学療法，大動脈周囲リンパ節転移，胃癌

はじめに

大動脈周囲リンパ節をはじめとした遠隔転移を伴う進行胃癌の治療成績は不良である[1)2)]．一方，高度進行胃癌に対する新たな治療戦略として術前化学療法（neo-adjuvant chemotherapy：以下NAC）への期待が高まっている[3)]．今回われわれは，腹部大動脈周囲リンパ節転移を伴う進行胃癌に対してPaclitaxel（以下PTX），Cisplatin（以下CDDP），S-1の3剤併用のNACが著効し，組織学的CRとなり，無再発5年生存を得た1切除例を経験したので若干の文献的考察を加えて報告する．

症　例

患者：68歳，男性．

主訴：下腹部痛．

既往歴：高血圧．

家族歴：特記事項なし．

現病歴：平成17年11月に下腹部痛を主訴に入院した．下部消化管内視鏡検査では異常なく，上部消化管内視鏡検査で胃体部後壁に腫瘍を認めた．また腹部CTで大動脈周囲リンパ節の腫大を認めた．

入院時現症：身長168cm．体重60kg．眼球結膜に黄疸なし．眼瞼結膜に貧血なし．表在リンパ節は触知しなかった．腹部は平坦，軟で，圧痛や腫瘤性病変は触知しなかった．Performance States（PS）は0であった．

入院時検査所見：血清総蛋白値の軽度低下を認める以外に異常値はなかった．CEA，CA19-9，CA125の腫瘍マーカーも基準値以内であった．

上部消化管造影（UGI）検査所見：胃体下部後壁に隆起陥凹病変を認めた．

上部消化管内視鏡（GIF）検査所見：胃体下部後壁に不整な隆起陥凹病変を認めた（Fig. 1a）．生検の結果，低分化腺癌と診断された．

腹部CT検査所見：腹腔動脈周囲を中心に，大動脈周囲リンパ節の腫大を認めた（Fig. 2a）．

治療経過：以上より，cT3，cN3，cH0，cP0，cM1，cStage IV（胃癌取扱い規約13版[4)]に拠る）の高度進行胃癌と診断し，外科切除のみでの根治は困難と考えた．治療成績を向上させる目的で術前化学療法が試みられていることを患者に説明し，その効果の可能性と副作用についての十分なinformed consentを行い，院内倫理委員会の承認を得て臨床試験としてNACを施行した．レジメンは諸家[5)6)]の3剤併用化学療法を参考とし，PTX 60mg，CDDP 25mgをday1，day8，day15に投与しday22は休薬，同時にS-1100mgをday1より3週投与し，その後1週休薬とした．全休薬期間は1

2012年10月9日受付　2012年10月20日採用
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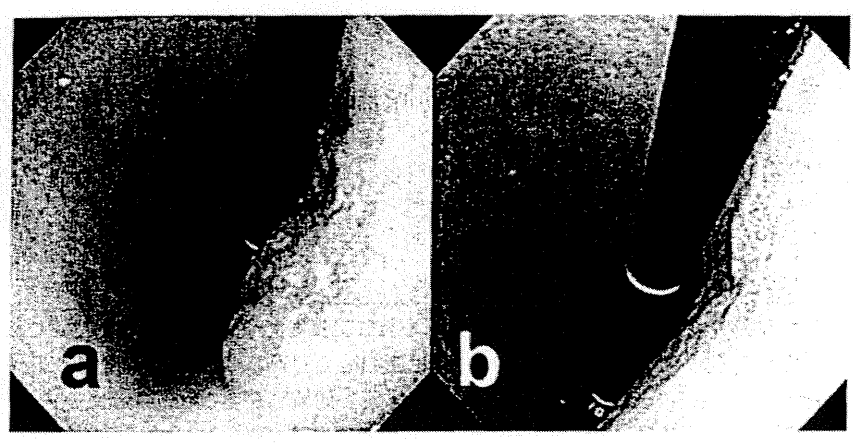

Fig. 1 : a) An endoscopic examination revealed a type 3 cancer in the posterior wall of lower body of the stomach. b) After four courses of neoadjuvant chemotherapy, it is a small depressed lesion of the stomach.

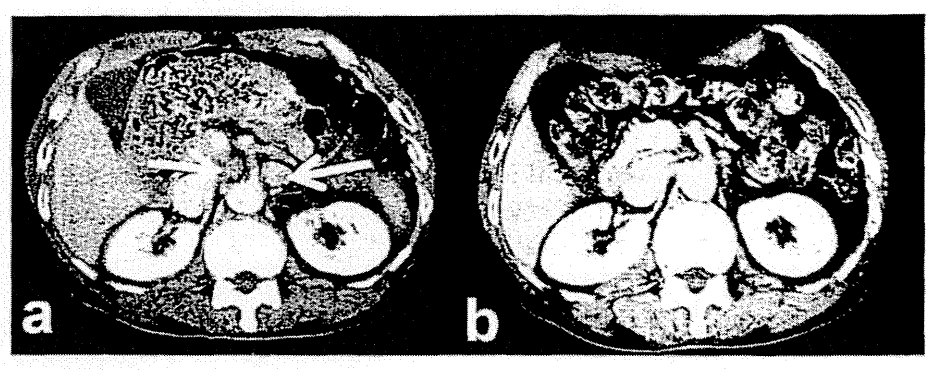

Fig. 2 : a) Enhanced CT scan demonstrated para-aortic lymphnode swelling (arrows). b) After four courses of neoadjuvant chemotherapy, para-aortic lymphnodes are reduced in size.

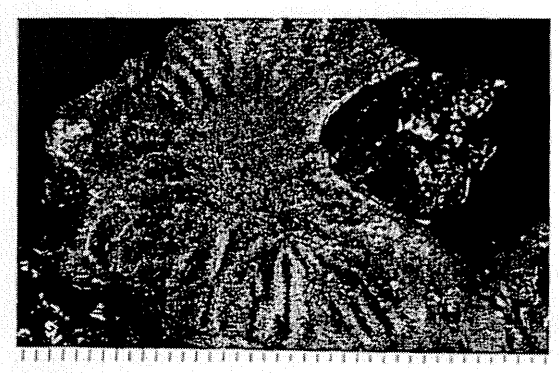

Fig. 3 : Resected specimen shows a small remnant ulcer in the posterior wall of the the gastric middle body.

週間とし，2コース終了後にGIFを施行した．腫瘍の縮小を認めたため，さらに2コース施行後にGIFと腹部CTを施行して効果判定を行った．なお化学療法の効果判定はRECISTガイドライン[7]を用いた．

効果判定UGI検査所見：胃体下部後壁の隆起陥凹病変は平坦化し，周囲との境界も不明瞭となっていた．

効果判定GIF検査所見：腫瘍は縮小し，平坦化していた(Fig. 1b)．生検組織診では癌細胞に核濃縮，膨化，多形性があり，壊死組織もみられ，化学療法の効果を確認した．

効果判定腹部CT検査所見：大動脈周囲リンパ節の縮小を認めた（Fig. 2b)．他に新たな転移を認めなかった．

以上よりNACが奏効したと判断し，術前化学療法終了1カ月後に幽門側胃切除（D2郭清）および左副

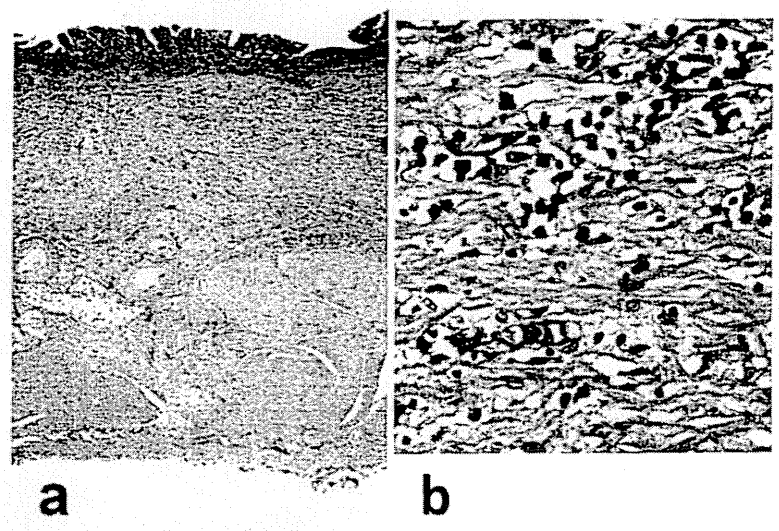

Fig. 4 : a) Histological examination of the resected specimen shows marked fibrosis accentuated in the submucosal layer in the primary gastric lesion (H.E. × 20).

b) Histological examination of the resected specimen also shows scattered inflammatory cell infiltrates but no residual cancer cells in the primary gastric lesion (H.E. × 400).

腎合併切除と大動脈周囲リンパ節郭清（No.16b1リンパ節，No.16a2リンパ節）を施行した．

切除標本肉眼所見：胃体下部後壁に浅い陥凹を認めるのみであった（Fig. 3）．

病理組織学的検査所見：主病巣の粘膜下層に広汎な線維化があり，固有筋層や漿膜下にも線維化が及んでいた（Fig. 4a，H.E.染色×20）．リンパ球や形質細胞の浸潤を認めるが癌細胞は認めなかった（Fig. 4b，H.E.染色×400）．大動脈周囲リンパ節は広汎に線維化し，リンパ組織の構築は消失しており，主病巣と同じく癌細胞は認めなかった．またNo.16b1の2個，No.16a2の12個を含む計30個の摘出リンパ節すべてに癌細胞を認めなかった．以上より組織学的効果判定はGrade3とした．

術後経過：術後6週後からS-1（80mg/body，4週投与2週休薬）を2年間投与し，5年間再発を認めていない．

考　察

高度のリンパ節転移を有する進行胃癌は，たとえ手術可能であったとしても予後不良である[1)2)]．特に大動脈周囲リンパ節転移陽性の胃癌症例は拡大リンパ節郭清を伴う手術を施行しても，3年生存率は5～10%程度とされる[3)]．その一方で，近年の胃癌化学療法の進歩により，胃癌治療の新たなstrategyとしてNACが提唱されている．NACは術後化学療法に比べてより強力な化学療法が施行可能であるため奏効率が高く，down stagingによる切除率の向上や腫瘍の縮小による多臓器合併切除の回避などが期待されるとされ[3)9)]，高度のリンパ節転移を有する進行胃癌に対して有効なstrategyと考えられる．現在S-1/CDDP併用療法は高度進行・再発胃癌に対する第一選択の化学療法として認められているが[10)]，NACとしても行われ，大動脈周囲リンパ節転移症例においての著効例も散見される[11)12)]．しかしNACの有効性を高めるにはさらに奏効率の高いレジメンを用いることが望まれ，S-1やDocetaxel（以下DOC）およびPTXのTaxane系抗癌剤，CDDP，Irinotecan などの併用療法が注目されている．このうちPTXは，細胞内の微小管の形成を安定化させることで細胞分裂を阻害し，抗腫瘍活性を示す[13)]．またPTXには腫瘍組織中のthymidine phosphorylase（PyNPase）を特異的に誘導することが報告されており，5'- deoxy 5fluorouridine（5'-DFUR）との併用療法により相乗効果が得られることが確認されている[14)]．PTXを併用した化学療法の有用性につ

Table 1. Reported cases of gastric cancer with para-aortic lymphnode metastasis in which both primary lesion and lymph nodes showed histological CR caused by NAC

Author	Year	Sex	Age	Type	Histologic type	Regimen	Course	Outcome (months)
Kiriyama[19]	2001	M	66	3	tub1	PMUE	2	unknown
Yabusaki[20]	2002	F	65	3	por	PLF	2	12M
Koizumi[11]	2003	M	60	3	tub2	S1/CDDP	1	8M
Matsuya[21]	2007	M	75	3	tub2	S1/DOC	3	15M
Fujisawa[22]	2007	M	60	3	por	S1/CDDP	2	12M
Matono[23]	2008	M	67	2	tub2	LowFP/CDDP→S1/CDDP	2+1	24M
Oshima[24]	2010	M	55	2	por	S1/CDDP	3	6M
Our case	2012	M	68	3	por	PTX/S1/CDDP	5	over 60M

PLF : CDDP+ Loicobolin + 5FU PMUE : CDDP+MMC+VP-16+UFT FP : 5FU+CDDP

いては，PTXとCDDPの併用が効果的であったとする報告[15]やPTX とS-1の併用が効果的であったとする報告[16]がみられる．自験例の化学療法導入時は，化学療法選択の指針が定まっておらず，種々の報告がなされていた．そのなかでAjaniら[17]がDOC/CDDP/5-FUのDCF療法がCDDP/5-FUのCF療法より良好であることを指摘していたため，われわれはより高い奏効率を期待して，3剤併用療法をNACに用いることとした．ただし3剤併用化学療法は副作用も強いと予想され，安全性が問題と考えられた．われわれは3剤併用化学療法のレジメンを選択するにあたり，当時当院においてtaxane系薬剤としてDOCよりもPTXを頻用していたこともあり，PTXを含むレジメンを検索し，岩瀬ら[5]の報告に注目した．しかしPTXとCDDPの量が多く，副作用が強いと判断した．そこでHaraら[6]の報告のPTX 80mg/m^2 (day1.8.15)/CDDP 25m/m^2 (day1.8.15)/5-FU600mg/m^2 (day1.8.15)の5FUをS-1 (100mg/body) に変更し，かつPTX，CDDPを減量したレジメンで施行した．自験例では化学療法による有害事象は認めず4コースを完遂できた．これにより十分な治療効果と根治的手術が可能であったと考えている．

大動脈周囲リンパ節転移陽性の1因子のみのStage IV胃癌に対するNACの有効性については多くの報告があり，上原ら[18]は1年生存率71.7%，2年生存率41.9%と報告している．しかし具体的なレジメンは確立されておらず，また同治療法が生存期間の延長に寄与するか否かについても明確なエビデンスは示されていない．医学中央雑誌で胃癌，大動脈周囲リンパ節，術前化学療法をキーワードとして1983年~2011年について検索したところNo.16リンパ節転移を伴う進行胃癌に対してNAC施行後に切除し，原発巣およびNo.16リンパ節ともにGrade3の組織学的効果判定を得た症例は7例報告されていた[11][19]~[24]．これら7例に自験例を含めた8例をTable 1に示す．年齢は55歳から75歳（平均64.5歳）で，男女比は7対1であった．癌の肉眼型は3型が6例，2型が2例であった．組織型は低分化型が4例と多かった．レジメンはS1/CDDPが3例，PMUE (CDDP/MMC/VP-16)，FLP (5FU/Leucovorin/CDDP)，S1/DOCが1例ずつで，1例がLow dose FP (5FU/CDDP) からS1/CDDPに変更した症例であった．施行数は2コースから3コースが多かった．なお術後5年生存の報告例は自験例のみであった．ところで自験例のように，NAC施行後にD2+No.16リンパ節郭清を行うか否かは議論のあるところである．JCOG9501[25]は壁深達度がT2 (SS) 以深で根治切除が可能な進行胃癌に対して，標準的D2郭清にNo.16リンパ節郭清を加えることの是非を問うた臨床試験であるが，結果はNo.16リンパ節郭清を加えた群と加えなかった群の2群間で5年生存率，無再発生存期間，再発形式に差はなかった．これにより治癒切除可能な進行胃癌に対する予防的No.16リンパ節郭清は否定され，D2郭清が標準術式とされた．自験例ではNACでdown stagingとなったが，もともと治癒切除困難例であったことと効果判定の目的もありNo.16リンパ節の郭清を施行した．また自験例のように組織学的CRを得た胃癌切除例における術後補助化学療法の是非も意見の分かれるところであるが，われわれは再発の可能性を考慮してS-1を減量して2年間投与した．

現在，根治切除不能高度進行胃癌に対するNACのレジメンとしてS-1 120mg/m² (day1-21) CDDP 60mg/m² (day8) が多く行われているが，最近DCSの報告もみられている[26]．また，高度リンパ節転移を伴う進行胃癌に対する術前DCS療法を検討したJCOG1002試験が進行中であり，その結果が期待されるが，自験例のように3剤併用療法の副作用を考慮してdose downした術前PTX/CDDP/S-1療法は有効と考えられた．

結　語

大動脈周囲リンパ節転移を認める高度リンパ節転移進行胃癌に対してPTX/CDDP/S-1のNACが著効し，組織学的CRとなり，無再発5年生存を得た1切除例を経験した．3剤併用療法の副作用を考慮してdose downしたPTX/CDDP/S-1のNACは有効と考えられた．

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A CASE OF GASTRIC CANCER WITH PARA-AORTIC LYMPHNODE METASTASIS RESPONDING TO PREOPERATIVE CHEMOTHERAPY COMPLETELY ON PATHOLOGY AND SURVIVING 5 YEARS WITHOUT RECURRENCE

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We report a case of gastric cancer with para-aortic lymphnode metastasis responding to preoperative chemotherapy (Paclitaxel (PTX)/Cisplatin (CDDP)/S-1) completely on pathology and surviving 5 years without recurrence. The patient was a 68-year-old man with advanced gastric cancer. Computed tomography (CT) scan showed para-aortic lymphnode metastasis. We thought a complete resection would be difficult, so he was given neoadjuvant chemotherapy combined with PTX, CDDP and S-1. After four courses of this neoadjuvant chemotherapy, both the tumor and the lymph node metastasis decreased in size. Radical resection was considered possible. He underwent distal gastrectomy with left adorenectomy and D2 + para-aortic lymph node dissection with curative intent. The pathological diagnosis revealed the complete disappearance of cancer cells in both the primary lesion of the stomach and lymph nodes, confirming a pathological complete response. The postoperative course was uneventful. The patient has been followed up for 5 years, including 2 years administration of S-1 with no evidence of recurrence. Advanced gastric cancer with para-aortic lymph node metastasis without other non-curative factors, can achieve long-term survival can be expected by combining a curative operation with PTX/CDDP / S-1 combined therapy.

Key words：neoadjuvant chemotherapy, para-aortic lymphnode metastasis, gastric cancer

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ORIGINAL ARTICLE

Is there diversity among *UGT1A1* polymorphism in Japan?

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Abstract

AIM: To investigate into the diversity of *UGT1A1* polymorphism across three different districts in Japan and highlight genetic differences among the population in Japan.

METHODS: We enrolled 50 healthy volunteers from each of the Yamaguchi (western part of Japan), Kochi (southern part of Japan) and Akita (northern part of Japan) prefectures. Blood samples (7 mL) were collected from each participant and stored in EDTA for subsequent genotyping by fragment size analysis, direct sequencing and TaqMan assay of *UGT1A1**28, *UGT1A7**3/*UGT1A9**22 and *UGT1A1**93/*UGT1A1**6/*UGT1A1**27/*UGT1A1**60/*UGT1A7* (-57), respectively.

RESULTS: The only statistically significant differences in allele polymorphisms among the group examined were for *UGT1A1*6*. The Akita population showed more *UGT1A1*6* heterozygosity ($P = 0.0496$).

CONCLUSION: Our study revealed no regional diversity among *UGT1A1*, *UGT1A7* or *UGT1A9* polymorphisms in Japan.

Key words: *UGT1A1* gene; Polymorphism; Diversity

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INTRODUCTION

Irinotecan with fluoropyrimidine is approved worldwide as a first-line chemotherapeutic agent for metastatic colorectal cancer[1-5]. Although prolonged survival has been reported with the use of this drug, severe diarrhea and neutropenia have also been reported as dose-limiting

toxicities in 20%-35% of patients treated by the agent. Recent studies revealed that the risk of such severe toxicities might be associated with genetic variation in irinotecan metabolism, indicating a possible predictive factor.

Irinotecan is activated by hydrolysis to SN-38, a potent topoisomerase I inhibitor[6] that is primarily inactivated through biotransformation into SN-38 glucuronide (SN-38G) by the enzyme uridine diphosphate glucuronosyltransferase isoform 1A1 (*UGT1A1*)[7]. In addition, the toxicity of irinotecan has been correlated with polymorphisms in the number of TA repeats in one of the promoter regions of the *UGT1A1* gene (*UGT1A1 *28*), which affects transcriptional efficiency[8]. Because of the clinical importance of the glucuronidation pathway in irinotecan treatment, *UGT1A1 *28* was proposed as a potent predictor for severe toxicity[9-11]. Recently, a novel prospective dose-finding study of irinotecan alone based on *UGT1A1*6* and **28* genotyping was reported[4,12]. These results showed that the *UGT1A1 *6* or **28* genotype status could be used to determine RD (recommended doses) of irinotecan. We conducted a prospective phase II study of FOLFIRI for metastatic colorectal cancer in Japan, analyzed the *UGT1A1*28* and **6* polymorphisms and demonstrated that the combination of the *UGT1A1*28* and **6* polymorphism is important to predict the adverse event of the CPT-11[5].

The role of *UGT1A1*28* alleles in the toxicity and pharmacokinetics of irinotecan is considerably different between Asians and Caucasians. Only homozygotes of **28* have been associated with neutropenia in Caucasians[11,13-15], whereas both homozygote and heterozygote **28* patients have shown severe toxicity with irinotecan in Japan[4,9]. Other results revealed that SN-38 glucuronidation was highly impaired in heterozygotes, as previously reported[9,16]. Such ethnic differences may be associated with other genetic variants of UGT1A family polymorphisms, such as *UGT1A1*60*, **6*, *UGT1A7*3* and *UGT1A9*22*, which were demonstrated in linkage disequilibrium experiments with *UGT1A1*28*[17-22]. Such genotype variation could affect SN-38 glucuronidation and also the severe irinotecan-related toxicity. This study aimed to clarify the regional differences in *UGT* enzyme polymorphisms among three different districts in Japan that are widely different, both geographically and culturally.

MATERIALS AND METHODS

The 50 volunteers from Akita, Kochi and Yamaguchi prefectures comprised of 8 males and 42 females, 6 males and 44 females, and 11 males and 39 females, respectively, with an average age of 37.5, 43.8 and 38.4 years, respectively. The examinee demographics are shown in Table 1.

Blood samples (7 mL) were collected from each participant and stored in EDTA for subsequent analysis. Examinees were limited to those whose parents and grandparents came from the same region.

Written informed consent was obtained from all participants.

Table 1 Examinee characteristics

	Akita	Kochi	Yamaguchi
Sex			
Male	8	6	11
Female	42	44	39
Age (yr)	37.4 (23-55)	43.8 (24-66)	38.4 (18-67)

Table 2 Primers, probes used for genotyping

Gene	Variant	Primers and probes[1]	
*UGT1A1*28*	-53 TA6/TA7	F-FAM	5'-gtgacacagtcaaacattaacttgt-3'
		R	5'-gcctttgctcctgccagaggtt-3'
*UGT1A7*3*	N129K	F	5'-tacactctggaggatcagga-3'
	W208R	R	5'-tattgggcatcacgggtttg-3'
*UGT1A9*22*	-118 T10/T9	F	5'-acttaacattgcagcacagg-3'
		R	5'-atgggcaaaagccttgaact-3'
*UGT1A1*93*	-3156 G/A	F	5'-cagaagggctagagaggaggaa-3'
		R	5'-cttgctctcaaaactctgggataga-3'
		FAM	5'-cctgtccaagctca-3'
		VIC	5'-cacctgtctaagctca-3'
*UGT1A1*6*	211 G/A		C 559715 20
*UGT1A1*27*	686 C/A		C 2307598 20
*UGT1A1*60*	-3279 T/G		C 1432134 10
UGT1A7 (-57)	-57 T/G		C 287265 10

[1]Primers for fragment size assay: F-FAM: Forward primer labeled FAM; R: Reverse primer. Primers for Sequence assay: F: Forward primer; R: Reverse primer. TaqMan assay: F: Forward primer; R: Reverse primer; FAM: Reporter 1 probe; VIC: Reporter 2 probe. Number: TaqMan SNP genotyping assays number.

Genotyping

Genomic DNA was extracted from peripheral blood anti-coagulated with EDTA-2Na, using a conventional NaI method[23]. *UGT1A1*28*, *UGT1A7*3*/*UGT1A9*22* and *UGT1A1*93*/*UGT1A1*6*/*UGT1A1*27*/*UGT1A1*60*/*UGT1A7* (-57) were genotyped by fragment size analysis, direct sequencing and TaqMan assay, respectively. Primers and probes used in this study are shown in Table 2.

For fragment size analysis, PCR reactions were performed in a total volume of 10 μL containing template DNA (80 ng/μL) according to the manufacturer's instructions (Ex Taq; Takara, Tokyo, Japan). The amplification was carried out with a Gene Amp PCR System PC808 (ASTEC, Tokyo, Japan), with an initial denaturation at 95 ℃ for 2 min followed by 27 cycles of denaturation at 94 ℃ for 30 s, annealing at 60 ℃ for 20 s, and extension at 72 ℃ for 30 s. The PCR products of TA6 and TA7, whose sizes were 94 *bp* and 96 *bp*, respectively, were mixed with Hi-Di formamide, including the internal size standard (GeneScan 500, Applied Biosystems, CA, USA) at a 1:10 (*vol/vol*) ratio. Then, samples were run in the ABI Prism 3100 Genetic Analyzer (Applied Biosystems). Fragment sizes were determined by comparison with the internal size standard (GeneScan LIZ-500) using the local Southern algorithm and the data were analyzed by GeneMapper™ software version 3.5 (Applied Biosystems).

For direct sequencing, PCR amplifications were performed using the Gene Amp PCR System PC808

Table 3 Polymorphisms of *UGT1A1* *n* (%)

	*UGT1A1**28 (*P* = 0.663)			*UGT1A1**6 (*P* = 0.0496)			*UGT1A1**27 (*P* = 1.000)			*UGT1A1**60 (*P* = 0.766)			*UGT1A1*-3156		
	6/6	6/7	7/7	A/A	G/A	G/G	A/A	C/A	C/C	G/G	T/G	T/T	A/A	G/A	G/G
A	41 (82)	8 (16)	1 (2)	1 (2)	20 (40)	29 (58)	0 (0)	0 (0)	50 (100)	2 (4)	19 (38)	29 (58)	1 (2)	8 (16)	41 (82)
K	37 (74)	13 (26)	0 (0)	0 (0)	14 (28)	36 (72)	0 (0)	1 (2)	49 (98)	1 (2)	25 (50)	24 (48)	0 (0)	13 (26)	37 (74)
Y	37 (74)	12 (24)	1 (2)	3 (6)	9 (18)	38 (76)	0 (0)	0 (0)	50 (100)	2 (4)	22 (44)	26 (52)	1 (2)	12 (24)	37 (74)

A: Akita prefecture; K: Kochi prefecture; Y: Yamaguchi prefecture.

Table 4 Polymorphisms of *UGT1A7* and *UGT1A9* *n* (%)

	UGT1A7 N129K (*P* = 0.853)			*UGT1A7* W208R (*P* = 0.409)			*UGT1A7* -57 (*P* = 0.409)			*UGT1A9**22 (*P* = 0.993)		
	G/G	T/G	T/T	C/C	T/C	T/T	G/G	T/G	T/T	9/9	9/10	10/10
A	7 (14)	24 (48)	19 (38)	2 (4)	23 (46)	25 (50)	2 (4)	23 (46)	25 (50)	5 (10)	24 (48)	21 (42)
K	8 (16)	20 (40)	22 (44)	4 (8)	17 (34)	29 (58)	4 (8)	17 (34)	29 (58)	6 (12)	22 (44)	22 (44)
Y	5 (10)	23 (46)	22 (44)	4 (8)	14 (28)	32 (64)	4 (8)	14 (28)	32 (64)	5 (10)	23 (46)	22 (44)

A: Akita prefecture; K: Kochi prefecture; Y: Yamaguchi prefecture.

(ASTEC, Tokyo, Japan) with Ex Taq polymerase. Amplification conditions were 30 cycles of 95 ℃ for 30 s, each annealing temperature for 20 s, and 72 ℃ for 30 s. PCR products were purified using ExoSAP-IT (Amersham Bioscience, Tokyo, Japan) for 20 min at 37 ℃ and then for 20 min at 80 ℃. Sequencing reactions were carried out using a BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Tokyo, Japan). After purification with ethanol, the reaction products were analyzed using an ABI 3100-Avant Genetic Analyzer (Applied Biosystems).

TaqMan assays of PCR products were performed according to the manufacturer's protocol. Specific forward/reverse PCR primers and TaqMan probes for *UGT1A1**93 were custom-synthesized by Applied Biosystems. Primers and probes for *UGT1A1**6, *UGT1A1**27, *UGT1A1**60, *UGT1A7* (-57) were purchased from Applied Biosystems (TaqMan SNP Genotyping Assays). Reaction mixtures were loaded into 384 well plates and placed in the ABI Prism 7900HT Sequence Detection System (Applied Biosystems). PCR amplifications were performed as follows: initial denaturation at 95 ℃ for 10 min, followed by 40 cycles of PCR with a denaturation at 95 ℃ for 15 s, and one step annealing/extension for 1 min at 60 ℃.

Statistical analysis and power calculation

Proportions of wild-type, hetero-type and homo-type were calculated with 95% Agresti-Coull confidence intervals (95% CI)[24]. Fisher's exact test with a two-sided significance level of 0.05 was used for comparing the areas. For a two-sided 95% CI for a binomial proportion whose true value is varied from 0.5 to 0.1, a sample size of 50 yields a half-width of, at most, 14% in any situations of the true value.

RESULTS

Tables 3 and 4 list the polymorphisms of *UGT1A1* allele *28, *6, *60, *27 and *93 (-3156), *UGT1A7* *3 (N129K, W208R, -57) and *UGT1A9**22. The incidence of wild-type *UGT1A1**28 in the Akita, Kochi and Yamaguchi cohorts was 82% (95% CI: 69 to 90), 74% (95% CI: 60 to 84) and 74% (95% CI: 60 to 84), respectively (*P*-value = 0.663). The incidence of homozygous *UGT1A1**28 across the three districts was only 1.3% (95% CI: 0.0 to 5.0).

The only statistical difference in allele polymorphisms examined among the three groups was in *UGT1A1**6. The incidence of wild-type *UGT1A1**6 across the Akita, Kochi and Yamaguchi populations was 58% (95% CI: 44 to 71), 72% (95% CI: 58 to 83) and 76% (95% CI: 62 to 86), respectively, while the incidence of heterozygous-type *UGT1A1**6 was 40%, 28% and 18%, respectively. Volunteers from Akita showed the most heterozygosity in *UGT1A1**6, although the *P*-value was 0.0496.

DISCUSSION

The participants in this study were mostly nurses and other medical staff from hospitals in the three Japanese prefectures. Around 95% of the nurses in Japan are women; thus the predominance of female subjects in this study.

There are several reports about the distribution of *UGT1A1* polymorphisms worldwide. However, these studies were limited to the promoter region, *UGT1A1**28[8,25-27], and demonstrated that *UGT1A1**28 homozygosity is frequent in Europe (5.0%-14.8%), Africa (5.9%-17.9%) and the Indian subcontinent (19.2%-24.0%), compared to East Asia, which comprises mainly of the Chinese (1.2%-5.0%)[25,26]. Hall *et al*[25] showed that sub-Saharan Africa, especially Cameroon, was 33% homozygous for

Figure 1 The location of the three prefectures. Akita represents the northern part of Japan, while the Kochi prefecture on Shikoku Island was obstructed from communication with other prefectures by the Shikoku mountain (dotted line) range in ancient times. Yamaguchi is one of the nearest prefectures to the Korean Peninsula in Japan.

*UGT1A1*28*, which is a fairly high frequency even compared to Caucasians and Indians.

The incidence of homozygous *UGT1A1*28* across the three districts of our data in Japan was only 1.3%, which is comparable to the 1.0% reported by Hall *et al*[25]. Premawardhena *et al*[26] also reported a wider diversity of repeat numbers among individuals from North and Central America with varying degrees of African ancestry. Our data demonstrated that the repeat number of (TA) was 6/6, 6/7 and 7/7, which is the same as those reported for Europeans and other Asians. Hitherto, no studies have investigated the regional diversity in *UGT1A1*-family polymorphism within one country, although our study now indicates that there is no diversity of *UGT1A1*28* polymorphism in Japan.

In this study, we selected the Akita, Kochi and Yamaguchi prefectures (Figure 1). Akita represents the northern part of Japan, while the Kochi prefecture on Shikoku Island was obstructed from communication with other prefectures by the Shikoku mountain range in ancient times. Thus, both prefectures have developed a unique dialect and less communication with each other historically. On the other hand, Yamaguchi is one of the nearest prefectures to the Korean Peninsula in Japan. All the prefectures chosen have also developed a unique culture.

Our study revealed no regional diversity of *UGT1A1*, *UGT1A7* and *UGT1A9* polymorphisms in Japan. Only *UGT1A1*6* showed a statistically significant difference among these three regions in Japan, with more G/A type in the Akita prefecture compared to the other two regions. However, the *p*-value for the *UGT1A1*6* polymorphism was marginal (*P*-value = 0.0496) and the statistical significance is easily changeable due to the selection of the sampling population. The number of *UGT1A1*6* homozygotes was not different among the three districts, with allele frequencies for Akita, Kochi and Yamaguchi of 2.2%, 1.4% and 1.5%, respectively.

Our study is an exploratory research about the diversity of *UGT1A1* in Japan. Before the study, we speculated that Akita may have the same tendency of *UGT1A1* polymorphism as Caucasians, i.e. Akita may have more polymorphism in *UGT1A1*28* and less polymorphism in *UGT1A1*6*. However, our study revealed that *UGT1A1*28* showed no diversity and *UGT1A1*6* did not show less polymorphism, although this was not random sampling and generalizability of our population could not be guaranteed.

As described, heterozygotes of *UGT1A1*28* are extremely rare in the Japanese population compared to Caucasians and the incidence of heterozygotes and homozygotes of *UGT1A1*28* across the three districts combined was 22.0% and 0.013%, respectively.

Our study also demonstrated that the *UGT1A1*6* polymorphisms, G/A and A/A, occurred at a rate of 28.7% and 2.7%, respectively, in Japan. Kaniwa *et al*[28] examined the variants of *UGT1A1*6* in Caucasian and African-American populations. Caucasians showed only two heterozygotes among 150 blood samples, while none were found among the African-Americans. Our study confirmed the Japanese standard data for *UGT1A1* polymorphism frequencies, which shows more variants for *UGT1A1*6* compared to Caucasian and African-American samples.

Jinno *et al*[29] examined the glucuronidation of SN-38, a potent inhibitor of topoisomerase 1, by human UGT1A1 variants in Cos-1 cells. The variant 211G<A (G71R) (*UGT1A1*6*) reduced the glucuronidation activity more than 686C>A (P229Q) (*UGT1A1*27*). Moreover, hyperbilirubinemia observed in Japanese and Taiwanese patients with the P229Q variant is mainly attributable to the TA7 variation. Thus, *UGT1A1*6* plays an important role during chemotherapy with irinotecan in East Asian populations[28,30].

Finally, the variant sequences in exon 1, *UGT1A1*6* and *UGT1A1*27*, have been identified only in the Japanese. Thus, Japanese studies could focus more on these two genotypes, which might be more closely associated with drug sensitivity in Japanese patients than in Caucasians[31-33].

Our ongoing studies will compare *UGT1A* gene polymorphism worldwide, starting in Asian populations and gradually spreading to Europeans. Such investigations may also clarify the movement of people throughout history.

COMMENTS

Background

Irinotecan with fluoropyrimidine is approved worldwide as a first-line chemotherapeutic agent for metastatic colorectal cancer. Although prolonged survival has been reported with the use of this drug, severe diarrhea and neutropenia have also been reported as dose-limiting toxicities in 20%-35% of patients treated by the agent. Recent studies revealed that the risk of such severe toxicities might be associated with genetic variation in irinotecan metabolism, indicating a possible predictive factor.

Research frontiers

This study aimed to clarify the regional differences in *UGT* enzyme polymorphisms among three different districts in Japan that are widely distant, both geographically and culturally.

Innovations and breakthroughs

The authors enrolled 50 healthy volunteers from each of the Yamaguchi (west-

ern part of Japan), Kochi (southern part of Japan), and Akita (northern part of Japan) prefectures. Blood samples were collected from each participant and stored in EDTA for subsequent genotyping by fragment size analysis, direct sequencing, and TaqMan assay of *UGT1A1**28, *UGT1A7**3/*UGT1A9**22, and *UGT1A1**93/*UGT1A1**6/*UGT1A1**27/*UGT1A1**60/*UGT1A7* (-57), respectively.

Applications

The authors found that the only statistically significant differences in allele polymorphisms among the group examined were for *UGT1A1**6. The Akita population showed more *UGT1A1**6 heterozygosity. This study revealed no regional diversity among *UGT1A1*, *UGT1A7* or *UGT1A9* polymorphisms in Japan.

Peer review

Kobayashi *et al* aimed to clarify the regional differences in UGT enzyme polymorphisms among three different districts in Japan that are widely distant, both geographically and culturally. The study seems interesting, but the sample size is somewhat small.

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