総論―消化器内視鏡診断の最前線

カプセル内視鏡

Capsule endoscopy

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【ポイント】

◆ カプセル内視鏡は，SB1 から SB2 への改良，FICE が使用できる RAPID®Access 6.5 の改良など，デバイスの著しい進歩がみられる．

◆ カプセル内視鏡は，原因不明の消化管出血だけでなく，クローン病や NSAID 小腸病変の検出，治療効果判定に対する有効性が報告されている．

◆ 将来的に食道用，大腸用，自走式，治療用カプセル内視鏡の実用化が期待されている．

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はじめに

カプセル内視鏡（capsule endoscopy：CE）は，Given Imaging 社により開発された消化管画像診断システムであり，2000 年に Nature 誌に発表されて以来，現在までに全世界で 100 万個以上使用されている[1]．現在は，2007 年より保険適用となった小腸用カプセル内視鏡のみ使用可能であるが，海外や一部のわが国の施設でも食道，大腸用カプセル内視鏡が使用され，将来的には非侵襲的かつ有用な検査として期待されている．本稿では，これらカプセル内視鏡について，適応や今後の展開について解説する．

カプセル内視鏡の概要

CE（PillCam®SB）は，大きさ 26 mm×11 mm の薬のカプセルのような形態であり（図 1），内服後より腸管蠕動により移動し，白色発光ダイオード LED（light emitting diode）が発光すると同時に CMOS（complementary metal-oxide semiconductor）イメージセンサーにより 2 フレーム/秒で画像を撮影し，無線で体外のデータレコーダーに送信する．送信されたデータは，RAPID® ワークステーションを用いて解析する．カメラの性能は，撮影範囲 156 度，最小検出能 0.1 mm，ビデオ倍率 8 倍である．また，RAPID®Access 6.5 より，分光画像処理機能（flexible spectral imaging color enhancement：FICE）が追加され，FICE 1，FICE 2，FICE 3 と 3 種類の FICE 設定が選択できるようになり（図 2），FICE 1，FICE 2 は angioectasia などの病変検出に有用であり，FICE 3 は胆汁などで見にくい画像の観察に有効である[2]．オリンパス社の CE（Endo Capsule）は，大きさは PillCam®SB と同形であり，撮影範囲は 145 度，高感度 CCD を使用している点に違いがある（図 3）．

検査方法としては，原則的に検査の 8 時間以上前より禁食とし，少量の水で CE を嚥下した後，約 8 時間後に検査が終了する．この方法による CE の全小腸観察率は 74.1％と報告されているが[3]，最近では検査時間の延長や工夫により，観察率は向上している．工夫としては，経口腸管洗浄剤などによる前処置や，消泡剤，prokinetics（消化管運動機能改善薬）などあるが，prokinetics の有効性がないとする報告や，逆に過剰促進により病変を記録する前に通過してしまうという報告もあり，その使用に関しては検査医の裁量に委ねら

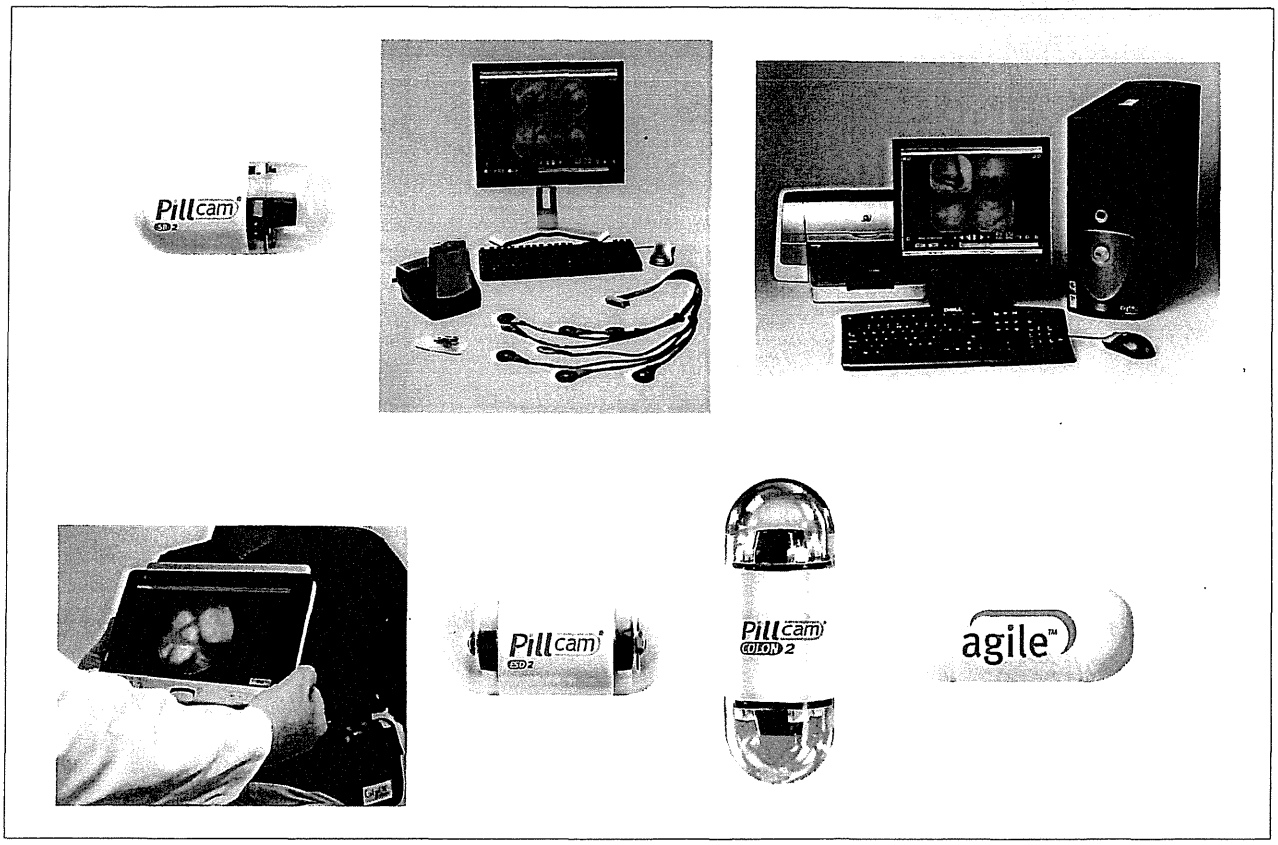


図1　カプセル内視鏡とギブン画像診断システム
上段：Given 社製小腸用カプセル内視鏡と RAPID® ワークステーション．
下段：左より RAPID® リアルタイム，食道用カプセル内視鏡，大腸用カプセル内視鏡，Patency Capsule．
（画像提供：Given Imaging 社）

れている．施設によっては検査開始1時間後にRAPID®リアルタイム（**図1**）により画像を確認して，CE の排泄促進する場合や，検査終了直前に画像を確認して，終了時間を延長（最長 15 時間以上）する場合もある．当院の症例では，検査時間 9 時間未満では全小腸観察率 66.8％であるが，9 時間以上では 85.2％，14 時間以上では 100％であった．CE の適応は原因不明の消化管出血であり，CE の禁忌は，心臓ペースメーカーなど電気医療機器が埋め込まれている患者や嚥下障害のある患者，クローン病や腹部手術後など CE の滞留の可能性がある患者である．滞留は 1.6％，海外でも 0.75～1.4％と報告されている．滞留の可能性がある症例に CE を施行する場合は，超音波検査，CT 検査，小腸造影や今後発売予定である Patency Capsule を先に行う必要性がある．

CE の臨床

■原因不明の消化管出血（obscure gastrointestinal bleeding：OGIB）

現在の保険適用疾患であり，その割合は全消化管出血の約 3～5％である．OGIB とは上部および下部消化管内視鏡検査にて，胃，十二指腸，大腸に出血源が同定できない出血を意味するが，再検査を行うと胃，十二指腸，大腸に出血源がある場合が 24.3％であったという報告もあり[4]，見逃しや予断には注意が必要である．OGIB の CE の診断能は約 70％であり，ダブルバルーン小腸内視鏡検査とほぼ同等である[5]．また，出血のエピソードから 2 週間以内に検査を行うと病変の検出率が有意に高い[6]．CE の出血所見は**図4**に示すような CE 出血分類により分けることができ[7]，胃潰瘍の Forrest の分類と同様に CE-Ⅰ，Ⅱ，Ⅲの順に再出血の可能性が高いため，当科では**図5**に示すアルゴリズムを用いて検査，治療を行っている．ちなみに出血源は，成人では，米国の場合 40％以上が血管性病変（血管拡張症）である一方[8]，日本では潰瘍あるいは炎

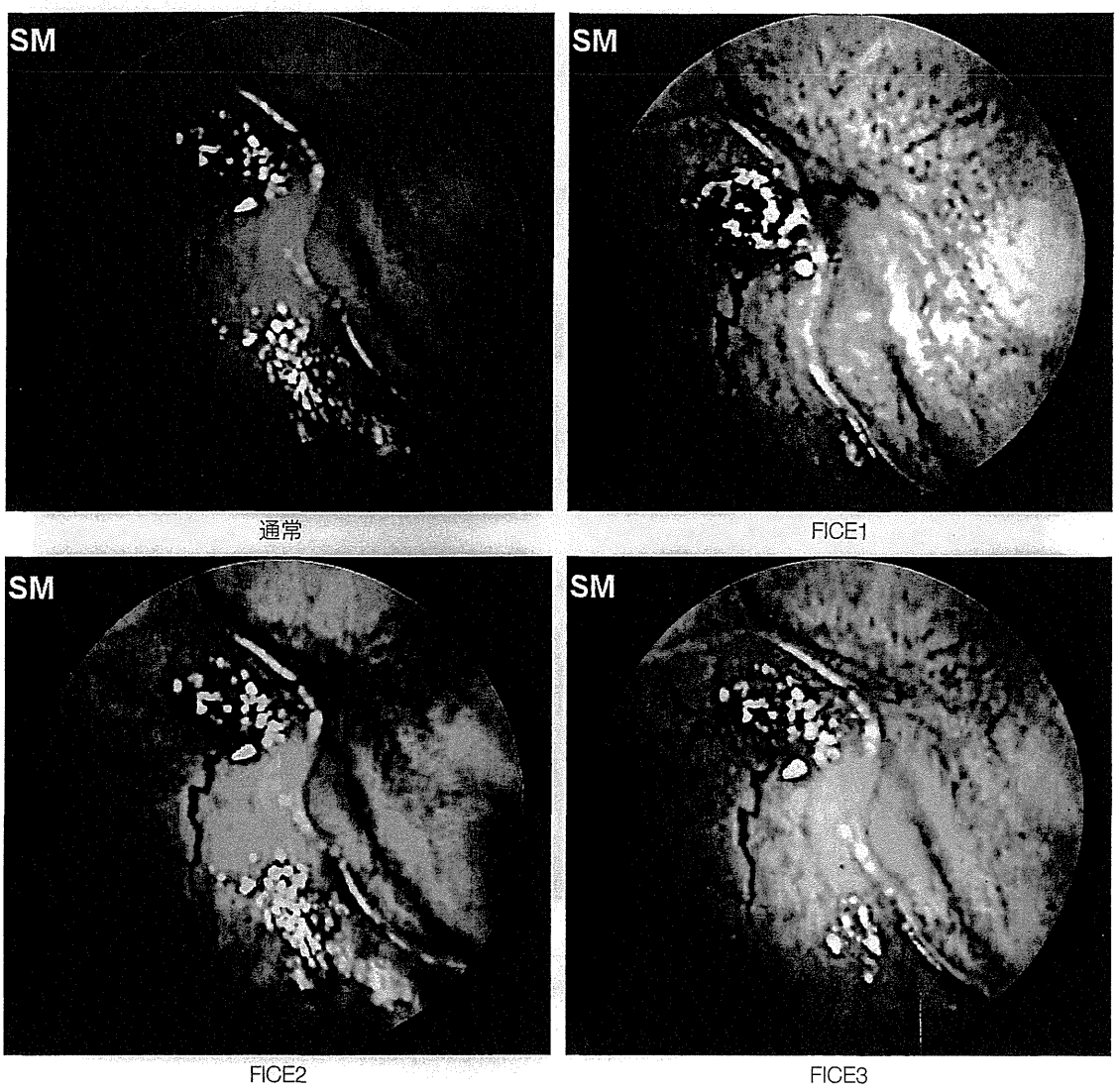


図2　カプセル内視鏡 FICE 画像（angioectasia）

症性病変（34.3%）が最も多く，ついで血管性病変（25.7%），腫瘍性病変（17.1%）の順であった[3]．40歳未満の症例では，日米ともにメッケル憩室，クローン病が多かった．

■NSAID による小腸粘膜傷害

NSAID（非ステロイド性消炎鎮痛薬）内服により，小腸粘膜傷害は50%以上にみられる[9]．したがって，NSAID 内服患者における原因不明消化管出血は，小腸粘膜傷害の可能性が高く，出血源の検索に CE は有効である．しかし，NSAID の粘膜傷害は，膜様狭窄を生じ，滞留の原因となるため，小腸造影などで狭窄の有無を確認して施行するほうが安全である．ちなみに治療や予防として，NSAID の内服中止，セレコキシブへの変更，レバミピドやミソプロストール投与が有効とされる．

■小腸腫瘍

小腸腫瘍は，原発性消化管腫瘍の6%，悪性腫瘍に限ると1～2%と稀な疾患である．小腸出血の原因の10%が腫瘍性病変であり，小腸腫瘍の70%が粘膜下腫瘍様病変である．小腸悪性腫瘍は，悪性リンパ腫，小腸癌，平滑筋肉腫，カルチノイドなどであり，良性腫瘍はほとんどがGISTである．CEの小腸腫瘍検出率は33%と高くないが（ダブルバルーン内視鏡は67%）[10]，当科での検討では CE を PET-CT 検査と併用することにより小腸腫瘍の検出感度100%，特異度90%，陽性的中率87.5%，陰性適中率100%に向上した[11]．CE は，PET-CT 検査など他のデバイスと併用すれば，さらに有用性が高まると考えられた．

■クローン病

現在，わが国ではクローン病患者への CE 使用は禁

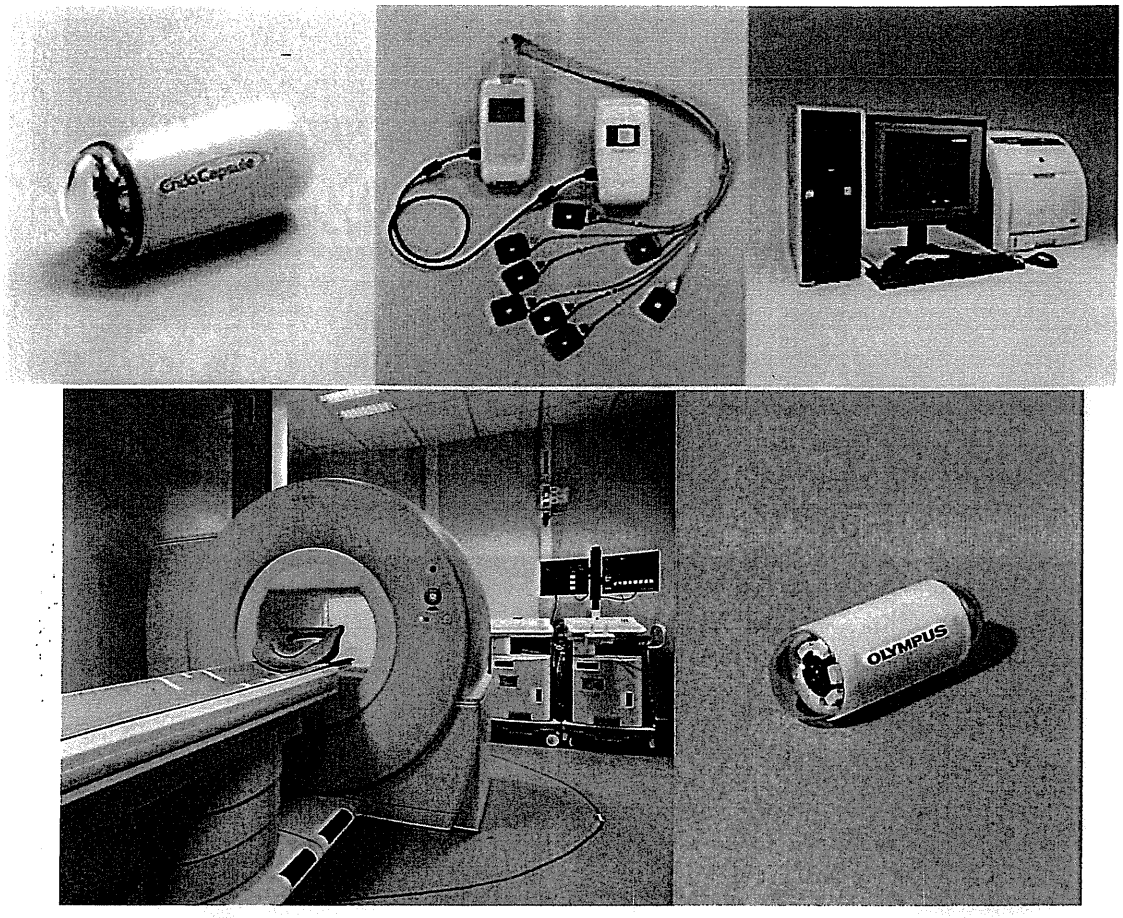


図3　カプセル内視鏡システム（オリンパス社）
上段：オリンパス社製小腸用カプセル内視鏡とワークステーション．
下段：磁気誘導で自在に動かせる胃観察用カプセル内視鏡．
（画像提供：オリンパスメディカルシステムズ）

忌であるが，海外，日本国内において，クローン病症例のCEの使用報告は多数みられる．CEにおけるクローン病の診断率についてみると，感度77%，特異度89%と報告されている[12]．CEの滞留の問題があるものの，Patency CapsuleやCT検査，超音波検査，小腸造影を併用すれば，滞留の可能性の少ない患者においては，クローン病の初期診断や治療の効果判定にCEは有用と考えられる．

将来の展望

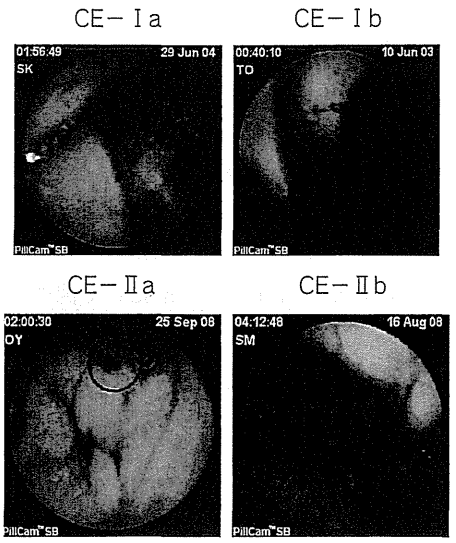
■食道用カプセル内視鏡

PillCam®ESOカプセル内視鏡（ECE）は2004年から米国で販売されており，大きさ11 mm×26 mm大，両側各1基の小型カラービデオカメラ，LED光源が装備された内視鏡である（**図1**）．患者がカプセルを嚥下した後，平均30分以内で検査終了となる．主に肝硬変患者の食道静脈瘤の評価に使用され，海外では約4,500万人以上に使用されている．さらに2011年5月23日にPillCam®ESO 3カプセル内視鏡（ECE-3）が，米国食品医薬品局（FDA）の承認を取得した．ECE-3は，電子部品や光学部品改良により，広角視野，毎秒35フレームの撮像速度など，旧製品と比べて著しい改善がみられる．わが国では，ECEはまだ臨床治験の段階であり，認可の目処は立っていない．

■大腸用カプセル内視鏡

PillCam®COLON 2カプセル内視鏡（CCE-2）は，大きさ11 mm×31 mm大，両側各1基の小型カラービデオカメラ，LED光源が装備された内視鏡である（**図1**）．患者がカプセルを嚥下した後，約10時間にわたって最大35枚/秒の画像が撮影され，記録装置に転送される．Spadaら[13]は，10時間の撮影で88%の患者が全大腸を観察でき，6 mm以上のポリープの検出感度84%，特異度64%，10 mm以上のポリープの検出感度88%，特異度95%，大腸癌の検出率100%（3/3）と報告してい

Type	所　見				
CE-0	所見なし				
CE－Ⅰ	活動性出血				
Ⅰa	噴出性出血				
Ⅰb	湧出性出血				
CE－Ⅱ	出血の可能性を示唆する病変				
Ⅱa	露出性血管，血餅付着，黒い潰瘍底				
Ⅱb	黒色，または暗赤色の凝血塊や便，腸液を認める				
CE－Ⅲ	出血所見のない病変				
	Ⅲu	Ⅲv	Ⅲt	Ⅲd	Ⅲo
	潰瘍，炎症性病変	血管性病変	腫瘍性病変	憩室	その他
CE－Ⅳ	小腸外病変				



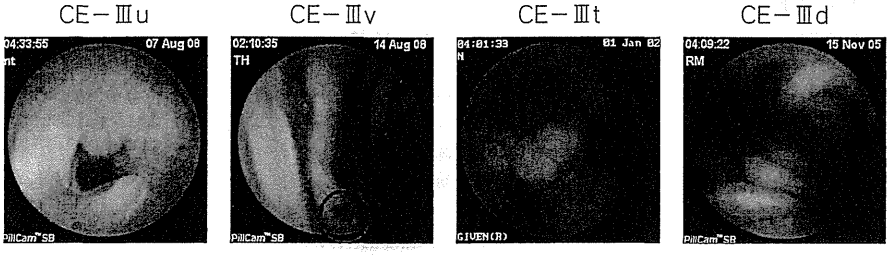


図 4　カプセル内視鏡（CE）出血分類（文献 10 より引用して改変）

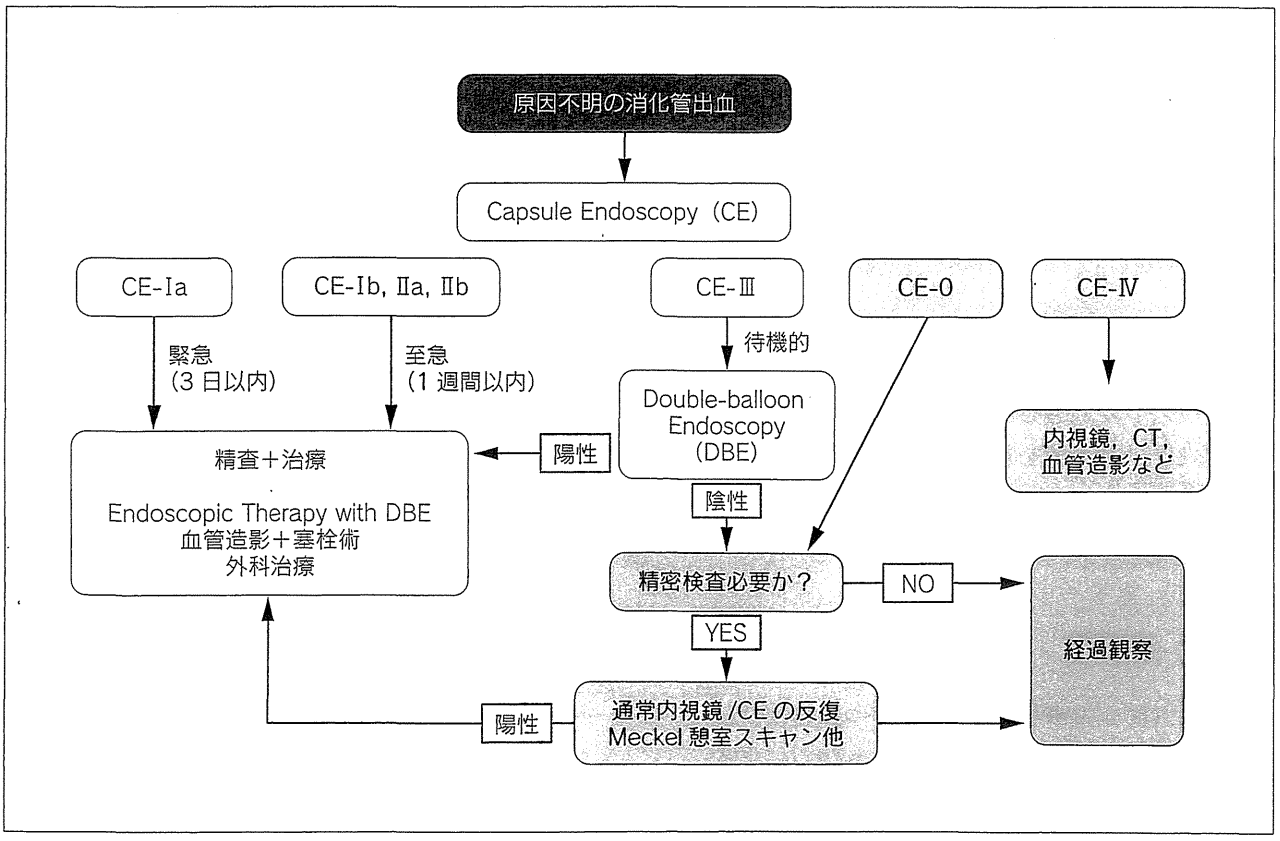


図 5　カプセル内視鏡出血分類による原因不明の消化管出血の診断と治療に対するアルゴリズム

る．わが国では現在，臨床治験が行われており，2012年頃に認可の予定である．

Patency Capsule

Patency Capsuleは，CEとほぼ同形であり，CE検査前に内服して消化管の開通性を確認するために用いられるカプセルであり，腸内で溶解する（図1）．海外の報告によると，Patency Capsuleで開通性を担保された症例の滞留率は0%であった．わが国でもタグの入っていないAgile-J Patency Capsule（AJP）が共同自主研究中である．

自走式カプセル内視鏡

Reyら[14]は，オリンパス社とシーメンス社が協同で開発した，磁場によりカプセル内視鏡を操作する装置を報告した（図3）．これはMRIに似た磁気誘導装置に患者を寝かせ，内服させたカプセル内視鏡を体外よりジョイスティックを用いて，磁気誘導により操作する仕組みとなっている．臨床試験の結果，胃幽門部，胃体部，胃底部，噴門部の観察率はおのおの98%，96%，73%，75%であった．また，龍谷大学理工学部と大阪医科大学が協同で開発した「マーメード」という愛称の自走式カプセル内視鏡も報告されている[15]．これは，従来のカプセル内視鏡に魚の尾びれのような駆動装置を装備したもので，尾びれは体外装置の強力な電磁石で動かすことができる．Given Imaging社も自走式カプセルを開発しており，現在人体で使用したと報告している．

治療用カプセル内視鏡

2008年にValdastriら[16]が，先端にニッケル/チタン合金性のクリップを装着したカプセル内視鏡を体外から無線操作し，止血処置を行ったと報告した．ほかにも薬剤を放出するCEなどが開発されている．現在はまだ研究段階であり，今後の発展が期待されている．

おわりに

今後さらにCEが進歩し，非侵襲的かつ操作性の良い検査に進歩すると考えられる．しかし，いくら非侵襲的な検査といえども滞留などの合併症の危険性があり，全身状態が悪く治療ができない患者への安易な使用は控えるべきであり，CEの役割と適応を十分理解して使用することが重要である．

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ORIGINAL ARTICLE

Phase II clinical study of DD-723 (perflubutane): dose–response study in patients with breast tumors

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Abstract
Purpose We compared the contrast effect of three doses of DD-723 in subjects with breast tumors to determine the recommended dose. We then evaluated differential diagnosis results using plain ultrasonography, contrast-enhanced ultrasonography (plain + enhanced), and contrast-enhanced magnetic resonance imaging (MRI) compared to the pathological diagnosis.

Methods To evaluate the contrast effect, contrast-enhanced ultrasonic images were independently evaluated in a randomized sequence by three blinded reviewers trained in the evaluation method beforehand. Multiple evaluation results from the three reviewers were used to assess the overall contrast effect. The differential diagnosis was evaluated independently by three blinded reviewers using contrast-enhanced ultrasonic images and contrast-enhanced magnetic resonance images in a randomized sequence; reviewers were also blinded to subject characteristics. Multiple evaluation results from the three reviewers were used to assess the overall differential diagnosis.
Results The recommended dose of DD-723 is an intermediate dose of 0.12 μL MB/kg. Accuracy, sensitivity, and specificity were improved more in the differential diagnosis by contrast-enhanced ultrasonography than in plain ultrasonography. Accuracy and specificity were better and sensitivity similar compared to contrast-enhanced MRI.
Conclusions An intermediate dose showed the highest efficacy in terms of overall contrast effect. Contrast-enhanced ultrasonography is safe and useful when used in differential diagnosis.

Keywords Ultrasound contrast medium · Breast tumors · Phase II clinical study · Sonazoid

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Introduction

DD-723 is a contrast medium for ultrasonic diagnosis produced by Nycomed from Norway (currently GE Healthcare AS). It is a freeze-dried product for injection that contains perflubutane, a chemically stable gas, with egg yolk phosphatidylserine and hydrogen in an internal capsule. By adding water for injection to this product

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before administration, a suspension of microbubbles with a mean diameter of 2–3 μm is formed, and a contrast effect is obtained when ultrasonic waves undergo efficient reflection and dispersion from intravascular microbubbles after this agent is administered intravenously.

Since this product circulates systemically via the capillaries, it can enhance the blood vessels of various organs. Therefore, it is expected to be useful and has been applied clinically for the detection of abnormal venous structures and mass lesions in the contrast phase.

Since primary liver cancer secondary to viral hepatitis is common in Japan and the liver is also frequently a site of metastasis, development was carried out in Japan to evaluate the diagnostic capacity of this product for hepatic mass lesions and its detection of hepatic mass lesions based on characteristic incorporation by Kupffer cells of the liver [1]. As a result, this product was approved in October 2006 with "contrast enhancement of hepatic mass lesions during ultrasonography" as the indication. It has been marketed since January 2007 under the brand name of Sonazoid® for Injection.

Since this product provides contrast enhancement of blood vessels in various other organs as well as the liver, as described above, the possibility of additional indications was studied.

In Japan, breast cancer is the most common cancer among women and about 40,000 new cases occur every year [2]. This number has been increasing every year and it is expected to exceed 50,000 women annually by 2020 [3]. The mortality rate is also increasing [4]. In the United States and Europe, the number of cases is higher than in Japan, but the mortality rate has tended to decrease in recent years [5]. This is considered to be due to early detection and treatment because of a high breast cancer screening rate of 60–80% [6]. However, the screening rate in Japan is currently about 10%, and this low rate presents a problem [6].

In the diagnosis of breast cancer, inspection and palpation are performed initially, with mammography and ultrasonography used for imaging diagnosis. For differential diagnosis of benign and malignant lesions and for assessment of the extent of lesions, contrast-enhanced magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT) are used, while the definitive diagnosis is done by pathological examination (cytodiagnosis and histodiagnosis).

Contrast-enhanced MRI and contrast-enhanced CT have problems related to lack of convenience and the need for caution in patients with reduced renal function. Contrast-enhanced CT is also associated with the problems of radiation exposure [7] and iodine allergy or shock.

Contrast-enhanced ultrasonography with this product will be useful for the differential diagnosis of benign and malignant breast lesions, assessing the extent of infiltration of lesions, and assessing the response of breast cancer to treatment. In comparison with contrast-enhanced MRI and contrast-enhanced CT, contrast-enhanced ultrasonography has the advantages of excellent spatial, temporal, and contrast resolution, as well as the ability to observe continuous real-time images during wash-in and wash-out of the contrast medium through the tumor vasculature. Since contrast-enhanced ultrasonography using this product is simple to perform, it is expected to become a new modality for the detailed examination of breast cancer.

Therefore, a dose–response study in patients with breast tumors was planned as a phase II clinical study to confirm the efficacy of this product for breast tumors and to investigate the optimum dose.

Subjects and methods

Subjects

The subjects were 86 patients who met all of the inclusion criteria, did not violate any of the exclusion criteria, and gave written informed consent of their own free will from among patients with breast tumors at five hospitals in Japan between April and December 2009. The study was approved by the institutional review boards of the hospitals and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

The inclusion and exclusion criteria were as follows. As described in the "inclusion criteria" section, subjects confirmed to have untreated masses (lesion of interest) and expected to undergo pathological examination were enrolled in the study. The benign/malignant nature of the lesion of interest was identified after performing the pathological examination. Therefore, no bias exists in subject enrollment. Subjects were registered and randomized by the central registration method.

Inclusion criteria:

1. Patients with untreated masses (lesions of interest) detected by plain ultrasonography.
2. Patients expected to undergo pathological examination (cytodiagnosis or histodiagnosis) of the lesion of interest.
3. Patients aged from 20 to 80 years when giving consent.

Exclusion criteria:

1. Patients with a history of allergy to eggs or egg products.
2. Patients with an arteriovenous shunt (right-left) in the heart or lungs.

3. Patients with serious heart disease.
4. Patients with serious lung disease.
5. Patients who were scheduled to undergo gastrointestinal investigations such as barium meal using a foaming agent or peritoneoscopic examination on the day of study drug administration.
6. Patients who are currently participating in another clinical study or who have done so within the past 180 days.
7. Patients who are pregnant, possibly pregnant, or breast-feeding.
8. Patients who are expected to undergo surgery between the time consent is obtained and the pathological examination is completed.
9. Patients who cannot undergo contrast-enhanced MRI (patients with pacemakers, etc.).
10. Patients who are receiving or are expected to receive treatments such as chemotherapy or radiation therapy between the time consent is obtained and the pathological examination is completed.
11. Patients with local recurrence of the lesion of interest.
12. Patients who are receiving or are expected to undergo examination using a contrast medium (iodinated contrast medium, MRI contrast medium, other ultrasonic contrast medium, etc.) from 2 days before until 2 days after administration of the study drug.
13. Patients who are expected to undergo pathological examination up to 2 days after administration of the study drug.
14. Patients who have previously undergone administration of DD-723 (Sonazoid® for Injection).
15. Any other patients who are considered to be unsuitable to participate in this clinical study by the investigator.

Methods

Ultrasonic imaging

Plain and contrast-enhanced ultrasonic imaging were performed using ultrasonography equipment with a built-in harmonic B mode and the images were recorded. Table 1 shows the recommended settings for ultrasonography.

The manufacturer, type of equipment, probe, and settings (mechanical index: MI, frame rate) for ultrasonography were recorded. After starting the examination, the imaging conditions (MI value, frame rate, focus, etc.) were not changed, as a rule.

For plain ultrasonography, one mass was selected as the lesion of interest, the probe was set over the center of this lesion, and images were obtained every 15 s and recorded. Next, the probe was placed in approximately the same position as that for plain imaging, and imaging was conducted in the harmonic B mode from 15 s before administration of the study drug. Imaging was continued for 1 min after study drug administration and contrast-enhanced images were recorded.

Table 1 Recommended settings for ultrasonography equipment

	Plain ultrasonography	Contrast-enhanced ultrasonography	
		Before study drug administration	After study drug administration
Ultrasonography equipment (manufacturer)	Aplio (Toshiba)/Logiq 7 (GE)/Logiq E9 (GE)/ ProSound α10 (Aloka)		
Imaging mode	Fundamental B mode Harmonic B mode	Harmonic B mode	
Mechanical index	Maximum acoustic pressure	0.1–0.4	
Focus site	Just below lesion		
Frame rate	–	–	5–21 fps

Dosage and evaluation method

In subjects with breast tumors, a single dose of 0.024, 0.12, or 0.36 μL MB/kg of DD-723 was administered into the antebrachial vein. For efficacy evaluation, the primary endpoint was the efficacy rate of the contrast effect obtained with each dose, and the recommended dose was investigated from the dose–response relation. Secondary endpoints included the evaluation of differential diagnostic capacity. Safety was also evaluated.

The efficacy evaluation was performed by six blinded reviewers (three each for randomized ultrasonic images and contrast MRI images).

Before evaluation was performed, a training session was held and the evaluation committee (using 15 subjects for training) met to confirm the reliability of the blinded reviewers in order to standardize evaluation among them and to ensure the reliability of the results. The images used for training were excluded from the efficacy analysis.

All patient characteristic information was blinded to the image reviewers, including age, familial history, findings by questioning, findings on inspection and palpation, findings on imaging, and results of pathological examination. The blinded reviewers separately evaluated the contrast effect on the images for each subject in randomized sequence.

Each of three blinded US reviewers separately reviewed the ultrasonography images for all the subjects except for

the training, and also each of three blinded MRI reviewers separately reviewed the MRI images for all the subjects except for the training. When there was a difference in the evaluation results among the three reviewers, the dominant result was used.

Contrast-enhanced MRI

Contrast-enhanced ultrasonography and contrast-enhanced MRI were performed within 30 days, with at least a 2-day interval, after the study drug was administered regardless of sequence.

The imaging condition was 1.5 T or more and the Gd product was used as the contrast medium. T1-weighted images, T2-weighted images, diffusion-weighted images, and dynamic MRI were done.

Pathological diagnosis

After study drug administration, contrast-enhanced ultrasonography, and contrast-enhanced MRI had been completed, cytodiagnosis or histological diagnosis was done for pathological testing.

Primary endpoint

Contrast efficacy rate evaluated by blinded reviewers:

Results of multiple evaluations by three blinded reviewers were used to assess the overall contrast effect as the primary endpoint. The contrast efficacy rate was calculated from the following expression: a/(a + b + c + d).

Evaluation criteria of contrast effect:

a: There were no artifacts that hindered diagnosis, and sufficient contrast enhancement of the lesion of interest and the surrounding blood vessels was obtained.

b: There were no artifacts that hindered diagnosis, but contrast enhancement of the lesion of interest and the surrounding blood vessels was insufficient.

c: Artifacts occurred or tissue enhancement by the contrast medium was too strong and it was difficult to assess the lesion of interest or the surrounding blood vessels.

d: A contrast effect was not obtained (incorrect imaging conditions, failure of the ultrasonography equipment, etc.).

Secondary endpoints

Results of multiple evaluations by three blinded reviewers were used for the overall differential diagnosis.

1. Taking the pathological diagnosis as the gold standard, the differential diagnostic capacity (benign vs. malignant) of plain ultrasonography, contrast-enhanced ultrasonography (plain + enhanced), and contrast-enhanced MRI was evaluated in comparison with the pathological diagnosis.
2. The differential diagnosis (benign vs. malignant) made by plain ultrasonography, contrast-enhanced ultrasonography (plain + enhanced), and contrast-enhanced MRI was evaluated.

Plain US images were exclusively stored on one DVD, and both plain and contrast-enhanced US images were stored on another DVD. The three blinded US reviewers individually reviewed the two DVDs separately to determine whether the lesion was benign or malignant. The three blinded MRI reviewers individually reviewed the contrast-enhanced MRI images to determine the malignant versus benign nature of the lesion. The sequence of the images was randomized for review by the three reviewers. The three reviewers reviewed the US/MRI images in different sequences.

Main evaluation criteria for differential diagnosis by contrast-enhanced ultrasonography [8]:

1. Benign
    a. No enhancement
    b. Homogeneous enhancement
    c. Clear vasculature or "tree-like branching" in the lesion
    d. Ring-shaped enhancement of peripheral blood vessels in the lesion
2. Malignant
    a. Heterogeneous enhancement with defect
    b. Heterogeneous enhancement without clear defect
    c. Linear, curled, meandering, or irregular vasculature in the lesion
    d. "Crab-claw"-like enhancement of peripheral blood vessels in the lesion
    e. Multiple vascular enhancements entering linearly toward the lesion from many directions
    f. Pulsation in the lesion

Evaluation criteria for differential diagnosis by contrast-enhanced MRI:

Assessment of differential diagnosis by the same methods as in routine diagnosis.

Safety endpoints

The safety endpoints were adverse events, laboratory tests, and vital signs within 2 days after administration of the study drug.

Results

Efficacy

As shown in Fig. 1, 86 subjects were randomized in this study, 83 of whom received the study drug (28 in the low dose group, 28 in the intermediate dose group, and 27 in the high dose group). The primary endpoint was analyzed in 67 patients (23 in the low dose group, 23 in the intermediate dose group, and 21 in the high dose group from the efficacy analysis set). The secondary endpoints (differential diagnosis) were analyzed in 66 subjects (22 in the low dose group, 23 in the intermediate dose group, and 21 in the high dose group), after excluding 15 subjects who were used for the training session and the evaluation committee meeting (five from each group). Subject demographics are shown in Table 2.

Primary endpoint

In the efficacy analysis set for analysis of the primary endpoint, the efficacy rate for the overall contrast effect was 26.1% [6/23, 95% confidence interval (CI) 8.1–44.0] in the low dose group, 95.7% (22/23, 95% CI 87.3–100.0) in the intermediate dose group, and 81.0% (17/21, 95% CI 64.2–97.7) in the high dose group (Table 3). The highest efficacy rate for overall contrast effect was found in the intermediate dose group, and the maximum response was seen at the intermediate dose [Cochrane–Armitage test using contrast coefficients (−2, 1, 1): $P < 0.001$].

Failure of visualization of not only the lesion of interest but also surrounding tissues has been taken into account for the calculation of efficacy rate.

From the above findings, the highest efficacy rate for overall contrast effect was achieved in the intermediate dose group, and the dose–response profile showed a maximal response at the intermediate dose.

Secondary endpoints

Tables 4 and 5 show the accuracy, sensitivity, and specificity of the differential diagnosis in the efficacy analysis set. Pathological examination of 66 subjects in the efficacy analysis set revealed a malignant tumor in 26 cases and a benign tumor in 40 cases.

The accuracy of the differential diagnosis in the efficacy analysis set was 90.9% (60/66, 95% CI 84.0–97.8) for contrast-enhanced ultrasonography (plain + enhanced), 78.8% (52/66, 95% CI 68.9–88.7) for plain ultrasonography, and 75.8% (50/66, 95% CI 65.4–86.1) for contrast-enhanced MRI. The difference in accuracy between contrast-enhanced ultrasonography (plain + enhanced) and plain ultrasonography was 12.1% (95% CI 2.3–22.0), while the difference from contrast-enhanced MRI was 15.2% (95% CI 3.8–26.5). Significant differences were found among the groups (McNemar's test: $P = 0.021$, 0.012), and the accuracy was improved by contrast ultrasonography.

The sensitivity of the differential diagnosis was 96.2% (25/26, 95% CI 88.8–100.0) for contrast-enhanced ultrasonography (plain + enhanced), 84.6% (22/26, 95% CI 70.7–98.5) for plain ultrasonography, and 96.2% (25/26, 95% CI 88.8–100.0) for contrast-enhanced MRI. The difference in sensitivity between contrast-enhanced ultrasonography (plain + enhanced) and plain ultrasonography was 11.5% (95% CI −0.7 to 23.8). No significant difference was found between the two groups (McNemar's test: $P = 0.083$). The difference in sensitivity between contrast-enhanced ultrasonography (plain + enhanced) and contrast-enhanced MRI was 0.0% (95% CI −10.7 to 10.7), so the sensitivity was the same.

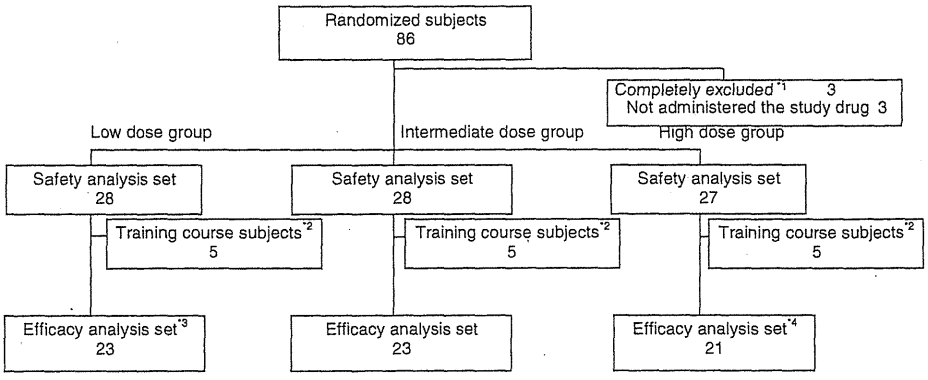

Fig. 1 Disposition of the subjects. *1The three patients were withdrawn from the study before study drug administration because they asked to leave the study for their own reasons. *2Subjects used for the training session and the evaluation committee meeting to confirm the reliability of the blinded reviewers. *3One subject was excluded from analysis of the secondary endpoints of differential diagnosis because the pathological diagnosis was unclear. *4One subject was excluded from the efficacy analysis because the subject had no recorded image

Table 2 Demographic and other baseline characteristics (efficacy analysis set)

Item	No. of subjects evaluated	Low dose group 23	Intermediate dose group 23	High dose group 21	All subjects 67
Age	<65	18 (78.3)	21 (91.3)	15 (71.4)	54 (80.6)
	≥65	5 (21.7)	2 (8.7)	6 (28.6)	13 (19.4)
	Mean ± SD	48.3 ± 16.0	51.2 ± 8.7	54.0 ± 13.2	51.1 ± 13.0
	Median	45.0	50.0	54.0	49.0
	Min, max	25, 74	34, 69	29, 74	25, 74
Body weight	<50 kg	9 (39.1)	6 (26.1)	7 (33.3)	22 (32.8)
	≥50 kg	14 (60.9)	17 (73.9)	14 (66.7)	45 (67.2)
	Mean ± SD	54.27 ± 12.60	55.13 ± 7.30	52.94 ± 7.37	54.15 ± 9.38
	Median	52.00	54.40	51.20	53.00
	Min, max	38.0, 104.0	40.6, 73.5	38.4, 70.0	38.0, 104.0
Treatment status	Inpatient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Outpatient	23 (100.0)	23 (100.0)	21 (100.0)	67 (100.0)
Size of the lesion of interest (long diameter)	<1 cm	9 (39.1)	4 (17.4)	6 (28.6)	19 (28.4)
	≥1 cm	14 (60.9)	19 (82.6)	15 (71.4)	48 (71.6)
	Mean ± SD	1.27 ± 0.73	1.52 ± 0.88	1.36 ± 0.57	1.38 ± 0.74
	Median	1.10	1.30	1.30	1.20
	Min, max	0.3, 3.4	0.4, 4.2	0.6, 2.6	0.3, 4.2
Pathological examination	Cytodiagnosis	2 (8.7)	4 (17.4)	4 (19.0)	10 (14.9)
	Histodiagnosis	21 (91.3)	19 (82.6)	17 (81.0)	57 (85.1)
	Both cytodiagnosis and histodiagnosis	3 (13.0)	1 (4.3)	1 (4.8)	5 (7.5)
Pathological diagnosis[a]	Malignant	10 (45.5)	7 (30.4)	9 (42.9)	26 (39.4)
	Benign	12 (54.5)	16 (69.6)	12 (57.1)	40 (60.6)

[a] For this subject (low dose group), the pathological specimen was not assessable. This subject was excluded from the differential diagnosis population for the secondary endpoint

Table 3 Overall contrast effect (efficacy analysis set)

Treatment group	a	b	c	d	Total	Efficacy rate[a] [95% CI]	Test[b]
Low dose	6 (26.1)	17 (73.9)	0 (0.0)	0 (0.0)	23	26.1 [8.1, 44.0]	$P < 0.001$
Intermediate dose	22 (95.7)	1 (4.3)	0 (0.0)	0 (0.0)	23	95.7 [87.3, 100.0]	
High dose	17 (81.0)	1 (4.8)	3 (14.3)	0 (0.0)	21	81.0 [64.2, 97.7]	

No. of subjects (%)

[a] Efficacy rate of contrast effect = a/(a + b + c + d)

[b] Cochrane–Armitage test using contrast coefficients (−2, 1, 1)

The specificity of the differential diagnosis was 87.5% (35/40, 95% CI 77.3–97.7) for contrast-enhanced ultrasonography (plain + enhanced), 75.0% (30/40, 95% CI 61.6–88.4) for plain ultrasonography, and 62.5% (25/40, 95% CI 47.5–77.5) for contrast-enhanced MRI. The difference in specificity between contrast-enhanced ultrasonography (plain + enhanced) and plain ultrasonography was 12.5% (95% CI −1.7 to 26.7), which was not significant (McNemar's test: $P = 0.096$). The difference in specificity between contrast-enhanced ultrasonography (plain + enhanced) and contrast-enhanced MRI was 25.0% (95% CI 8.4–41.6). There was a significant difference between the two groups (McNemar's test: $P = 0.008$), and specificity was greatly improved by contrast ultrasonography.

Although contrast-enhanced ultrasonography (plain + enhanced) showed no significant differences from plain ultrasonography, the overall differential diagnostic capacity was improved in all dose groups (100% sensitivity in the intermediate dose group for both examinations). In comparison with contrast-enhanced MRI, there were no significant differences from the low and intermediate dose groups, but the high dose group showed a significant difference. In all contrast-enhanced ultrasonography groups, the accuracy and specificity were improved while the sensitivity remained the same.

The above results indicate that the differential diagnostic capacity of contrast-enhanced ultrasonography (plain + enhanced) is good. In comparison with plain ultrasonography, the accuracy, sensitivity, and specificity are all improved, while the accuracy and specificity are improved and the sensitivity is the same when compared with contrast-enhanced MRI.

Safety

All 83 subjects who received the study drug (28 in the low dose group, 28 in the intermediate dose group, and 27 in the high dose group) were included in the safety analysis set.

Table 4 *Overall differential diagnosis: number of subjects with benign and malignant lesions (efficacy analysis set)*

Treatment group Pathological examination	All subjects		
	Malignant	Benign	Total
Contrast-enhanced ultrasonography			
Malignant	25	5	30
Benign	1	35	36
Total	26	40	66
Plain ultrasonography			
Malignant	22	10	32
Benign	4	30	34
Total	26	40	66
Contrast-enhanced MRI			
Malignant	25	15	40
Benign	1	25	26
Total	26	40	66

The overall incidence of adverse events was 6.0% (5/83). The incidence of adverse events was 7.1% (2/28) in the low dose group, 3.6% (1/28) in the intermediate dose group, and 7.4% (2/27) in the high dose group. Adverse events included headache, diarrhea, and rash in two subjects from the low dose group (headache and rash in the same subject), injection site pain and malaise in one subject from the intermediate dose group, and upper abdominal pain and injection site pain in one subject each from the high dose group.

The overall incidence of adverse drug reactions was 4.8% (4/83). The incidence was 7.1% (2/28) in the low dose group, 3.6% (1/28) in the intermediate dose group, and 3.7% (1/27) in the high dose group. The adverse drug reactions were diarrhea and rash in one subject each from the low dose group, and injection site pain in one subject each from the intermediate and the high dose groups.

The severity of adverse events was mild in all cases. Upper abdominal pain was treated, but the other events recovered without treatment. No serious adverse events were observed.

Discussion

For evaluation of contrast effect in this study, contrast-enhanced ultrasonic images were independently evaluated in a randomized sequence by three blinded reviewers who received training in the evaluation method beforehand, and the results of multiple evaluations by the three reviewers were used to assess the overall contrast effect. The overall contrast effect in the efficacy analysis set (the primary endpoint) was 26.1% (6/23) in the low dose group, 95.7% (22/23) in the intermediate dose group, and 81.0% (17/21) in the high dose group. The highest efficacy rate was found in the intermediate dose group, and maximum efficacy at an intermediate dose of 0.12 μL MB/kg was confirmed [Cochrane–Armitage test using contrast coefficients (−2, 1, 1): $P < 0.001$].

For assessment of the differential diagnostic capacity, contrast-enhanced ultrasonic images and contrast-enhanced MRI images were independently evaluated in a randomized sequence by three blinded reviewers. The results of multiple evaluations by the three reviewers were used for overall evaluation (three blinded reviewers each for the ultrasonography and MRI evaluations).

Table 5 Overall differential diagnostic capacity (efficacy analysis set)

Statistic (%) (95% CI)

Treatment group	Overall differential diagnostic capacity	Contrast-enhanced ultrasonography	Plain ultrasonography	Contrast-enhanced MRI
All subjects	Accuracy	90.9 (84.0, 97.8)	78.8 (68.9, 88.7)	75.8 (65.4, 86.1)
	Sensitivity	96.2 (88.8, 100.0)	84.6 (70.7, 98.5)	96.2 (88.8, 100.0)
	Specificity	87.5 (77.3, 97.7)	75.0 (61.6, 88.4)	62.5 (47.5, 77.5)

低分化進行胃癌

画像所見

50歳台，女性．胃癌検診で異常を指摘された．臨床検査データでは異常所見なし．

図1は，通常検査における前壁二重造影像で，胃角前壁に不整な陥凹面が見られる．図2-Aは切除標本との対比を理解しやすくするためのシェーマである．図2-Bは図1を180°回転した状態で陥凹面にバリウムを溜めた写真である．胃角小彎から前壁にかけて，辺縁が鋸歯状のバリウム斑が見られる（図2-B；病変範囲→）．IIc型胃癌の粘膜面の所見である．しかし，小彎側の浅い陥凹にはバリウムは均一に溜まっているのに対し，大彎に近い部分では幅の広い環状隆起が陥凹周囲に認められ，隆起成分が目立つ．この隆起成分を認める部分では，表面性状はIIcであっても深達度は進行癌の所見である．つまり，同じIIcの粘膜性状を示しながら一つの病変内に高さ（壁の厚み）のちがう部分があるということになる．

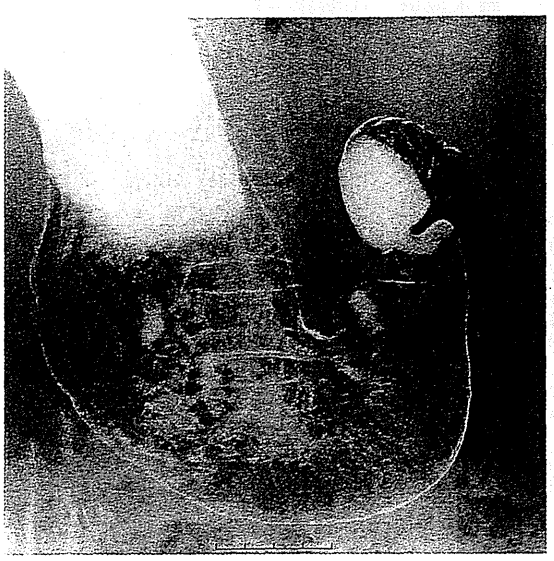

図1　前壁の二重造影像

病理所見

標本は幽門側部分切除されている（図3）．病変部は管状，篩状構造をとる腺癌で，粘膜内は比較的分化のよい中分化管状腺癌tub 2（図4）であるが，深部浸潤部を中心に低分化となっており，粘液産生の高度な粘液結節も混在している．

優勢度から，por 2＞tub 2＞mucである．主病巣では固有筋層までの浸潤であるが，リンパ管浸潤が漿膜下組織にあり，病変の最深部となっている．

A　　B　バリウム像

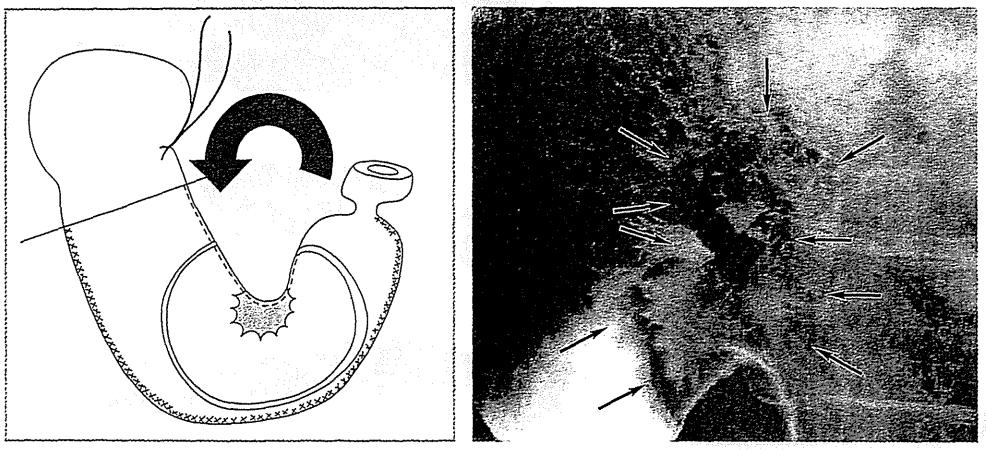

図2　前壁二重造影のシェーマ像（A）とバリウムを溜めたX線像（B）
図1のX線像を青矢印の方向に180°回転すると，図2-Bと同じ位置のX線像となり，固定標本との対比が容易である．

画像と病理像との対比

図5はX線像と割面ルーペ像を対比させたもので，X線像のABCの割面は固定標本と対応している．病変の最も大彎よりの割面Aでは低分化癌と粘液結節による隆起が示されているが，X線像は全体に隆起したIIc型進行癌の所見である．これに対し，最も小彎寄りの割面Cでは粘膜に限局したIIcであり，X線像では均一なバリウム斑として撮影されている．割面Bでは両者が混在し，左側に割面Cと同じIIc，右側に割面Aと同じ深部浸潤した隆起が認められる．X線像では同じようなIIcの表面性状をもっていても，深達度の浅いIIc部分ではバリウムが均一に溜まるのに対し，癌浸潤で隆起した部分ではIIc内にバリウムが溜まることができず，撮影のタイミングによっては単なる隆起に見える（図1）ので，注意が必要である．

■文献

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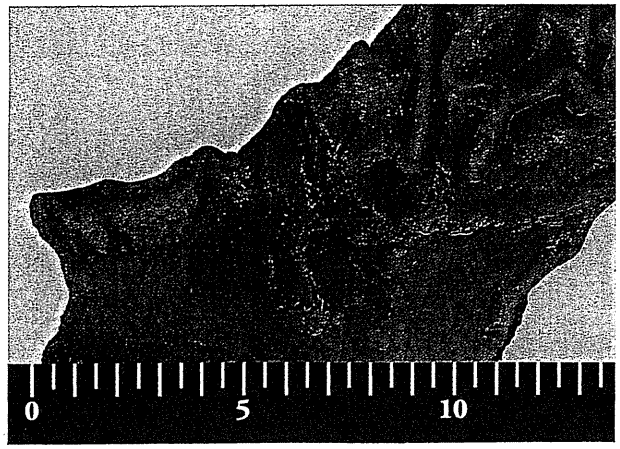


図3　固定切除標本

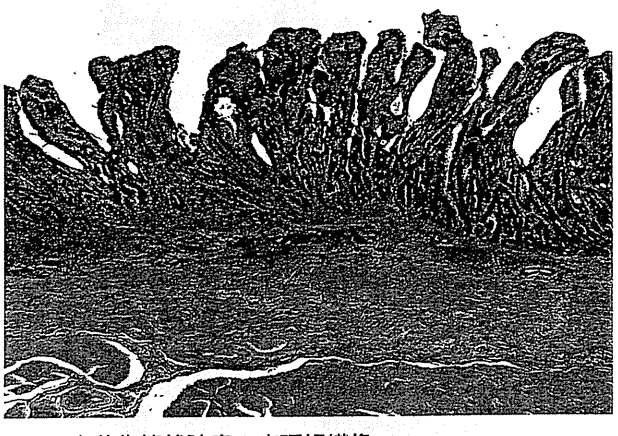
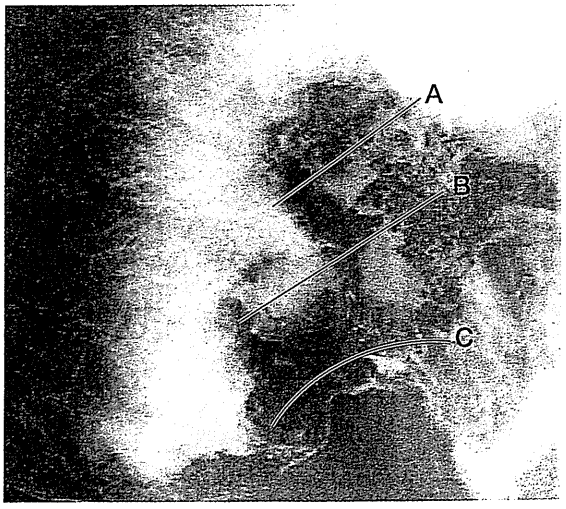


図4　中分化管状腺癌の病理組織像



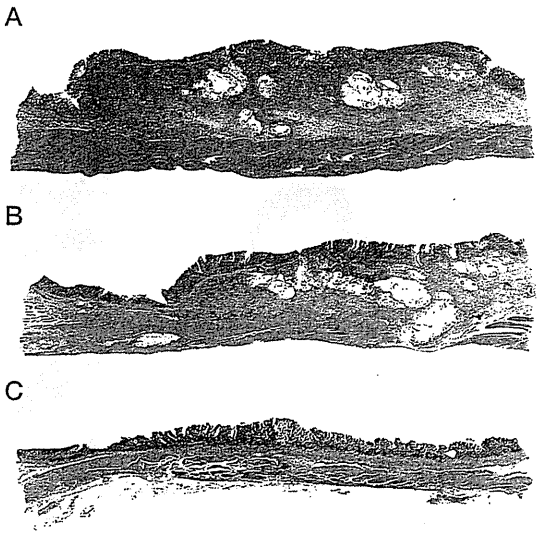


図5　X線像と割面ルーペ像との対比

十二指腸癌

画像所見

60歳台，女性．主訴は黄疸（褐色尿，皮膚掻痒感，皮膚黄染）．血液生化学検査では，肝胆道系酵素およびCA19-9の上昇を見る（T-Bil 12.31mg/dl，D-Bil 8.13mg/dl，CA19-9 149.16U/ml）．

CTでは，総胆管拡張が肝内胆管拡張および胆嚢の腫大を伴い下部胆管まで連続して見られ，十二指腸乳頭開口部直前でrat tail状に狭窄している（図1）．主膵管径は4～5mmと軽度拡張（図1；➪）．十二指腸下行脚の壁肥厚（図1，2；➡）とこれと接する膵頭部の淡い濃染域が観察される（図2；➡）．図2の→は膵内胆管を示す．病変の主座は十二指腸にあり，主膵管は膵頭部頭側方向へ牽引され，先細りした総胆管の先端部分は淡く濃染し，同程度に濃染した膵の領域に含まれている．以上の所見から，十二指腸癌が最も疑われ，膵への直接浸潤に伴う下部胆管閉塞が黄疸発症の原因と考えられる．また，病変部十二指腸の周囲脂肪織濃度上昇が見られ，これが近傍を走行する横行結腸（図1，2；T）と密に接しており，横行結腸浸潤が疑われる．

病理所見

新鮮切除標本（図3）では，十二指腸Vater乳頭（図3；→）の口側に周堤の不明瞭な潰瘍を形成する長径23mm大の3型の十二指腸癌を見る．肉眼的には，膵および横行結腸間膜への浸潤が疑われる．組織学的検索にて，癌の浸潤は十二指腸の固有筋層を越え，膵への浸潤（図4，5：➡）および膵内胆管（図4，5；→），横行結腸間膜の脂肪織に浸潤しており，腺腔の明瞭な小型～中型～大型の管状腺管を形成する中分化型管状腺癌の浸潤性増殖が認められる（図5）．

画像と病理像との対比

CT像（図1，2）と病理像（図3～5）とを対比し，腫瘍進展域のCT上の画像所見について検討する．

図1　造影CT冠状断像（早期相）

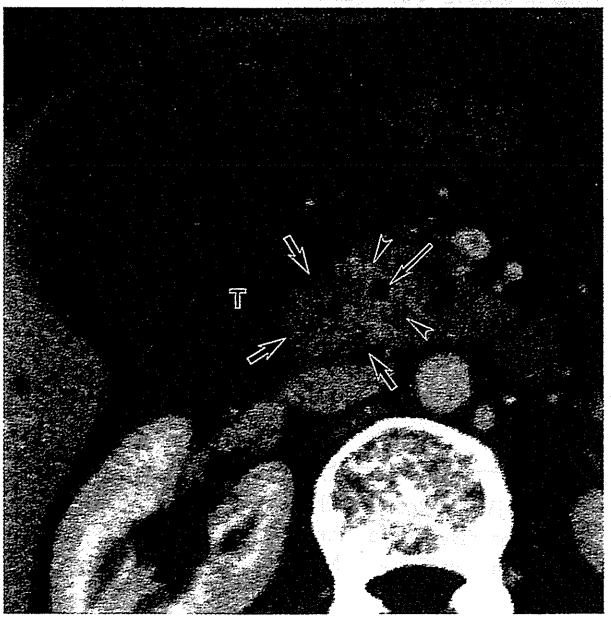


図2　造影CT（門脈相）

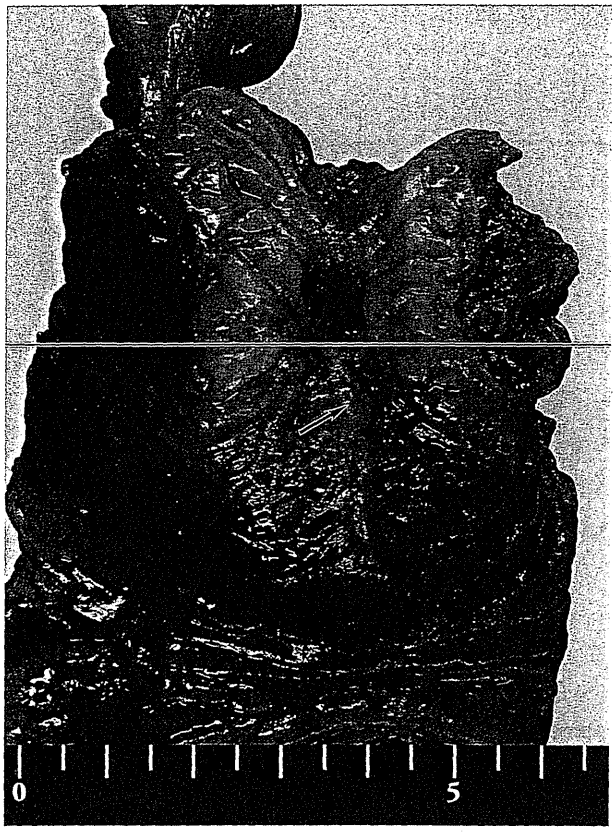


図3　切除標本

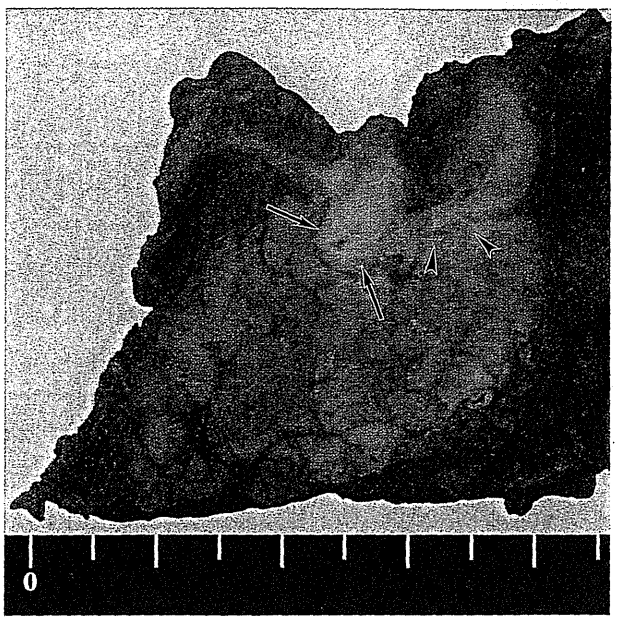


図4　図3のラインで示した部位での割面像

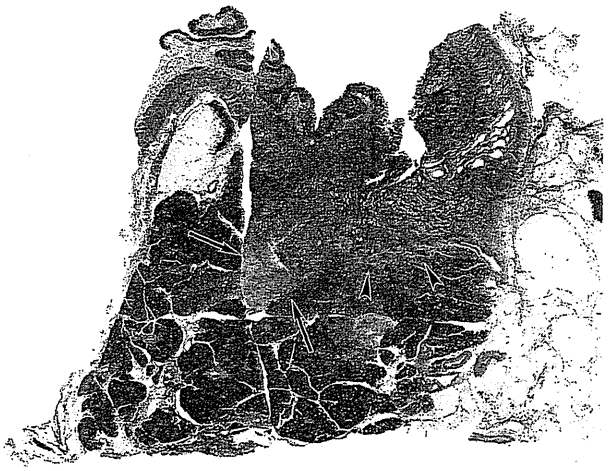


図5　図4の病理組織像

十二指腸の原発巣は下行脚の造影効果を有する壁肥厚域として同定される．周囲脂肪織への進展部分は脂肪織濃度上昇としてとらえられている．腫瘍が十二指腸壁を越えて膵へ直接浸潤している領域は，十二指腸と膵との境界不整，および十二指腸腫瘍部と接する膵頭部の背景膵より淡く染まる不整形領域として描出されている．

本症例の鑑別診断として，膵癌，下部胆管癌，Vater乳頭癌などが挙がるが，病変の主座は十二指腸にあり，膵病変は背側膵に存在するが主膵管拡張の軽微なこと，膵内胆管の所見が乏しいこと，Vater乳頭の腫大の見られないことなどが鑑別のポイントになる[1) 2)]．

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A case of long-term survival of metastatic desmoplastic small round cell tumor treated with multimodal therapy

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Abstract. Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive and malignant tumor that predominantly affects young males. No standard therapy is currently available for patients with DSRCT and the prognosis remains extremely poor. In this study, we report a thought-provoking DSRCT case. A 24-year-old male was admitted to our hospital with a chief complaint of hematemesis. Computed tomography revealed a retrovesical mass with a splenic hilar tumor, multiple lung and liver tumors and marked lymph node swellings. The source of hematemesis was gastric varices caused by the compression of the splenic vein by a splenic hilar tumor. The patient was provided with a histological diagnosis of DSRCT based on needle biopsy from the liver tumors and the pelvic mass was thought to be the primary lesion. This is a long-term survival case of metastatic DSRCT treated with multimodal therapy including 15 courses of multiagent chemotherapy, radiation therapy for the hepatic portal region using 42.5 Gy, and four instances of therapeutic endoscopy. The prolonged progression-free survival period (15 months) obtained following chemotherapy suggests the chemosensitive feature of the disease. We used a modified P6 regimen (cyclophosphamide, pirarubicin, vincristine, ifosfamide and etoposide) and a modified PAVEP regimen (cyclophosphamide, pirarubicin, etoposide and cisplatin) to decrease severe adverse events and to improve the completion rate of chemotherapy. DSRCT is an aggressive but chemo-sensitive disease, and continuous chemotherapy using an appropriate regimen with possible supportive care is essential for long-term survival. This case report may represent a treatment option for this rare disease.

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Key words: desmoplastic small round cell tumor, multimodal therapy, P6 regimen, PAVEP regimen

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive, malignant tumor that predominantly affects young males at a median age of 19 years (range 7-58) and with a male-to-female ratio ranging from 5:1 to 10:1 (1,2). DSRCT is a member of the small round blue cell tumor family, which includes small-cell carcinoma, Merkel cell carcinoma, synovial sarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, neuroblastoma, lymphoma, rhabdomyosarcoma and DSRCT (3). No standard therapy is currently available for patients with DSRCT and the prognosis of DSRCT remains extremely poor (2). In this study, we report a case of long-term survival of metastatic DSRCT treated with multimodal therapy, including multiagent chemotherapy, radiation therapy and therapeutic endoscopy.

Case history

A 24-year-old male was admitted to our hospital with a chief complaint of hematemesis. The patient had neither significant medical history nor family history. Physical examination revealed only that the patient was anemic. Laboratory examination was as follows: hemoglobin, 11.4 g/dl (normal range 13.5-16.7 g/dl); white blood cell count, 6,200/dl (normal range 2,900-8,900/dl); platelet count, 13.2×10^{10}/dl (normal range, $15.9-38.9 \times 10^{10}$/dl); C-reactive protein, 0.1 mg/dl (normal value ≤0.2 mg/dl); aspartate aminotransferase, 52 IU/l (normal range 13-33 IU/l); alanine aminotransferase, 99 IU/l (normal range 8-42 IU/l); alkaline phosphatase, 588 IU/l (normal range 115-359 IU/l); γ-glutamyl transpeptidase, 380 IU/l (normal range 9-54 IU/l); and total bilirubin, 0.7 mg/dl (normal range 0.3-1.3 mg/dl). Renal function tests were normal.

Endoscopy showed oozing bleeding from varicose veins located on the greater curvature of the upper gastric body (Fig. 1A). Spontaneous hemostasis was obtained. Computed tomography (CT) demonstrated that compression of the splenic vein by the splenic hilar tumor appeared to cause the gastric varices (Fig. 1B). CT revealed the presence of a well-enhanced, bulky and lobulated mass on the pelvic floor (Fig. 1C) with a splenic hilar tumor, multiple liver and lung tumors, and marked lymph node swellings (particularly in

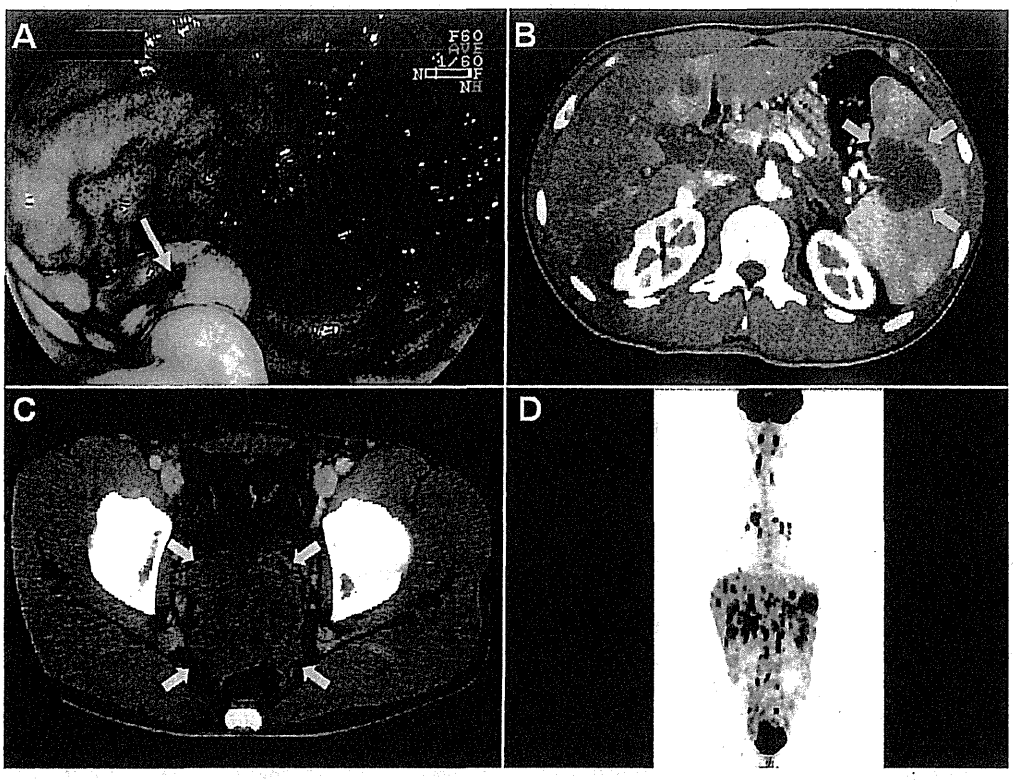

Figure 1. Endoscopic and radiological findings on admission. Endoscopy showed oozing bleeding from gastric varices (A, arrow shows bleeding point). Compression of the splenic vein by the splenic hilar tumor appeared to cause the gastric varices (B, arrows). A well-enhanced, bulky and lobulated tumor located on the pelvic floor was thought to be the primary lesion (C, arrows). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography revealed intense FDG uptake in the same tumors detected using computed tomography (D, a primary lesion, a splenic hilar tumor and multiple liver, lung and lymph node lesions).

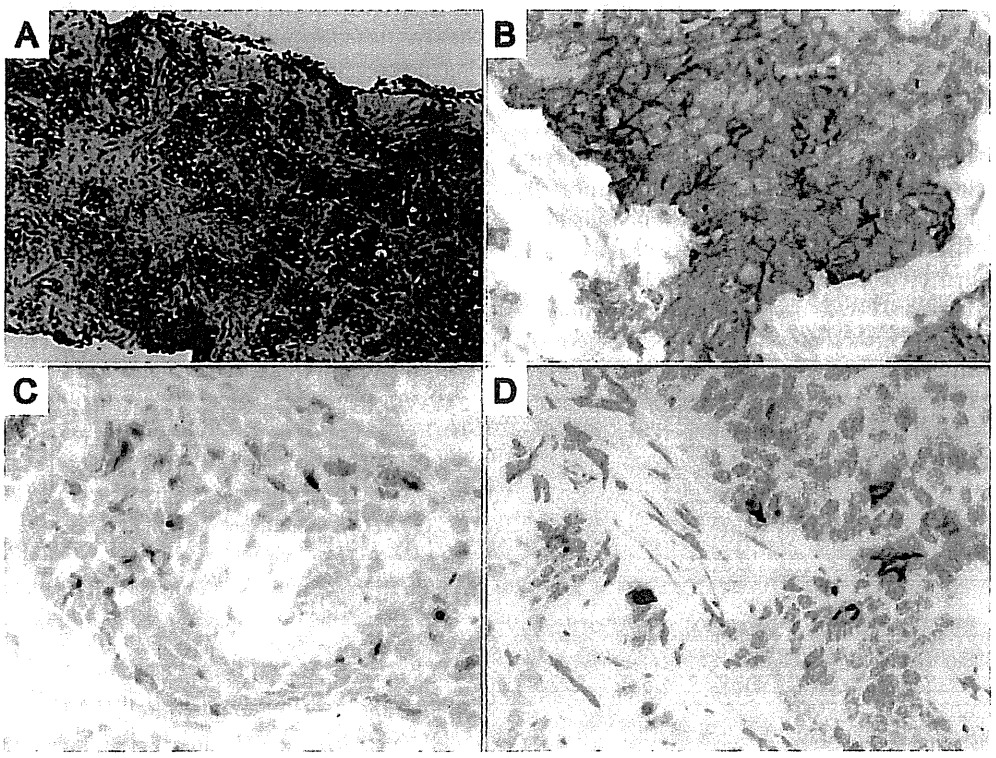

Figure 2. Representative pathological features of a needle biopsy specimen from the liver tumor. Hematoxylin and eosin staining showed poorly differentiated tumor cells with variable size and shape, composed of nests of small round cells and surrounded by a prominent desmoplastic stroma (A, magnification, x100). Immunohistochemical staining was positive for (B) cytokeratin (magnification, x400), (C) desmin (magnification, x400) and (D) Wilms' tumor 1 protein (magnification, x400).

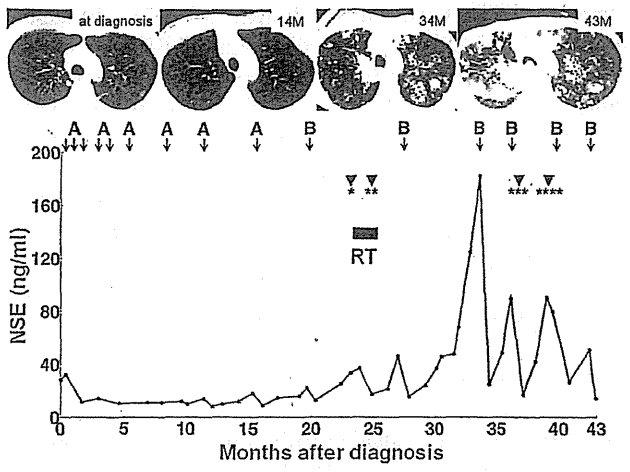

Figure 3. Clinical course of this case. Serum NSE level correlated well with clinical response. The patient received (A) nine courses of a modified P6 regimen and (B) six courses of a modified PAVEP regimen. Obstructive jaundice caused by portal lymphadenopathy was treated successfully by repeated endoscopic biliary drainage and radiation therapy (RT) to the hepatic portal region using 42.5 Gy, at 1.8 Gy per fraction. Massive hematemesis caused by active bleeding from the varicose vein was treated successfully by endoscopic hemostasis. The patient succumbed to acute pulmonary failure caused by progressive pulmonary metastases 43 months following diagnosis. Time-series CT images of pulmonary metastases are shown in parallel in the upper column (M, months after diagnosis). *Endoscopic biliary drainage using a plastic stent; **endoscopic biliary drainage using a metal stent; ***endoscopic hemostasis using metal clips for the active bleeding from a varicose vein; ****the metal stent obstruction caused by tumor ingrowth was relieved by inserting a plastic stent into the prior metal stent. NSE, neuron-specific enolase.

the hepatic portal region). ^{18}F-fluorodeoxyglucose positron emission tomography showed multiple accumulation of a glucose analog in the same lesions detected using CT (Fig. 1D).

A needle biopsy specimen from the liver tumor revealed the presence of a poorly differentiated tumor with a variable size and shape, composed of nests of small round cells surrounded by a prominent desmoplastic stroma (Fig. 2A). Immunohistochemically, tumor cells coexpressed an epithelial marker (cytokeratin, Fig. 2B), a mesenchymal marker (desmin, Fig. 2C) and the Wilms' tumor 1 protein (Fig. 2D). Chromogranin, cluster of differentiation antigen (CD) 99 and CD56 were negative. From these findings, the patient was provided with a definite diagnosis of pelvic cavity-origin DSRCT with multiple-organ metastases (4,5).

The clinical course of this case is shown in Fig. 3. The patient was initially treated with multiagent chemotherapy using cyclophosphamide, pirarubicin, vincristine, ifosfamide and etoposide, according to the Ewing's sarcoma protocol, which is a modified protocol of the P6 regimen using pirarubicin instead of doxorubicin (modified P6 regimen) (2,6). During each course of this chemotherapy, the patient suffered from severe nausea and vomiting. The patient required frequent blood transfusions and continuous use of granulocyte colony-stimulating factor due to severe bone marrow suppression. The multiple pulmonary metastases were almost eradicated following four courses of the modified P6 regimen and the patient reached 15 months of progression-free survival after the application of this modified P6 regimen (Fig. 3). After

Table I. Chemotherapy regimens reported previously and used in this case.

	Dose	Day
P6 (6)		
Courses 1, 2, 3 and 6		
Cyclophosphamide	2.1 g/m^2	1-2
Doxorubicin	25 mg/m^2	1-3
Vincristine	0.67 mg/m^2	1-3
Courses 4, 5 and 7		
Ifosfamide	1.8 g/m^2	1-5
Etoposide	100 mg/m^2	1-5
PAVEP (7)		
Doxorubicin	40 mg/m^2	1
Cyclophosphamide	300 mg/m^2	1-3
Etoposide	75 mg/m^2	1-3
Cisplatin	100 mg/m^2	4
Modified P6		
Courses 1, 3, 5 and 7		
Cyclophosphamide	2 g/m^2	1-2
Pirarubicin	20 mg/m^2	1-3
Vincristine	2 mg/m^2	1
Courses 2, 4 and 6		
Ifosfamide	2.5 g/m^2	1-5
Etoposide	100 mg/m^2	1-5
Modified PAVEP		
Pirarubicin	40 mg/m^2	2
Cyclophosphamide	450 mg/m^2	1-2
Etoposide	110 mg/m^2	1-2
Cisplatin	100 mg/m^2	1

Courses started after confirmation that the neutrophil count reached 500/μl and that the platelet count was >10,000/μl.

the nine courses of treatment, second-line chemotherapy based on the PAVEP regimen (doxorubicin, cyclophosphamide, etoposide and cisplatin) (7) was introduced due to disease progression. To reduce adverse events, we modified the PAVEP regimen by using pirarubicin instead of doxorubicin and shortening the period of the regimen from five to two days (modified PAVEP regimen). The P6, modified P6, PAVEP and modified PAVEP regimens are shown in Table I.

Obstructive jaundice caused by portal lymphadenopathy developed 23 months following diagnosis. Endoscopic biliary drainage using a plastic stent was successfully performed. However, stent obstruction occurred two months after the initial placement of the plastic stent. Subsequently, we removed the stent and inserted a metal stent, which was followed by irradiation of the hepatic portal region using a total dose of 42.5 Gy, at 1.8 Gy per fraction. The patient had massive hematemesis 37 months following diagnosis caused by the active bleeding from a known varicose vein and endoscopic hemostasis using