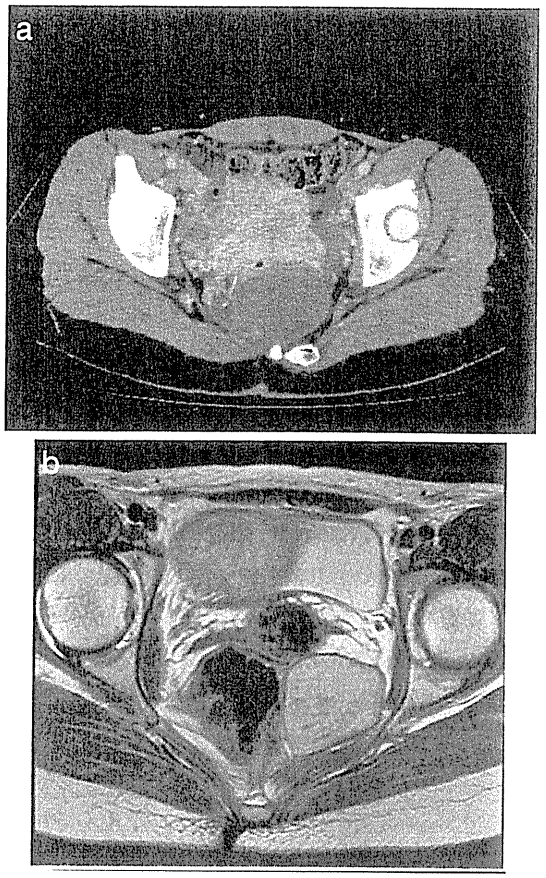

Fig. 1　症例1の画像所見
a：腹部骨盤造影CT．直腸左側に境界明瞭で造影効果のない腫瘤性病変を認めた．
b：骨盤MRI検査（T2強調画像）．直腸左側に位置する高信号を示す内部が均一な腫瘤性病変を認めた．

診断し，経仙骨的腫瘍切除術，尾骨合併切除術を施行した．

手術所見：全身麻酔下でJack-knife positionとし，超音波下に腫瘍の位置を確認した．仙骨左外縁より1横指外側に，仙骨外縁に沿い7 cmの皮膚切開を置いた．腫瘍は境界明瞭であったが，周囲の組織との癒着は強固であった．視野を確保するため尾骨を切除し，尾骨肛門靭帯を切離して腫瘤を摘出した．切除部を生理食塩水で十分に洗浄してドレーンを留置し，手術を終了した（Fig. 2a-c）．

切除標本（腫瘍割面）：単房性の厚い被膜を有する嚢胞性病変であった．

病理組織検査：多量の角化物を容れる嚢胞で，嚢胞壁には表皮類似の重層扁平上皮が認められた．皮膚付属器の混在は認めなかったことから類皮嚢腫（以後Epidermoid cyst）と診断した（Fig. 3a，b）．

術後経過は良好で，術後7日目に退院した．術後1年10ヵ月が経過しているが排便機能に問題なく，また再発は認めていない．

症例2：28歳，女性．

主訴：なし．

既往歴：特記すべきことなし．

現病歴：近医で骨盤内腫瘤を指摘され，精査・加療目的に当科を紹介され受診した．

入院時現症：自覚症状はなし．血圧105/58mmHg，脈拍62/分，整．体温36.4℃．眼瞼結膜，眼球結膜に貧血，黄染なし．表在リンパ節の腫大はなく，腹部は平坦，軟で腫瘤や圧痛などの異常所見を認めなかった．

入院時検査所見：血算，生化学検査に異常値を認めず，腫瘍マーカーもCEA 0.5ng/m*l*，CA19-9 11U/m*l*，AFP 1 mg/m*l*と正常範囲内であった．

腹部骨盤CT検査：下部直腸の左側に径6 cm大の腫瘤性病変を認めた．造影検査では腫瘤内部に増強効果を認めず，壁肥厚や隔壁構造も認めなかった．

骨盤MRI検査：下部直腸左側にT2強調像で高信号，ガドリニウム造影で内部に造影効果を認めない内部が均一な腫瘤性病変を認めた（Fig. 4a）．

大腸注腸造影検査および大腸内視鏡検査：下部直腸の軽度圧排像を認めたが，粘膜面に明らかな異常所見を認めなかった．

以上の検査所見より，前仙骨部の嚢胞性腫瘍と診断し，経仙骨的腫瘍切除術，尾骨合併切除術を施行した．

手術所見：全身麻酔下でJack-knife positionとし，超音波下に腫瘍の位置を確認し，肛門から約3 cmはなして仙骨左外縁の1横指外側に8 cmの皮膚切開を置いた．腫瘍径が大きかったため尾骨を切除し，さらに皮膚切開をV字型に右側に延長して視野を確保し腫瘤を摘出した．切除部を生理食塩水で十分に洗浄後，ドレーンを留置して手術を終了した．

切除標本（腫瘍割面）：単房性の厚い被膜を有する嚢胞性病変であった（Fig. 4b）．

病理組織検査：多量の角化物を容れる嚢胞であり，嚢胞壁には表皮類似の重層扁平上皮が認められた．皮膚付属器の混在はなく，Epidermoid cystと診断した．

術後経過は良好であり，術後7日目に退院した．術後8ヵ月経過しているが，排便機能障害や再発は認めていない．

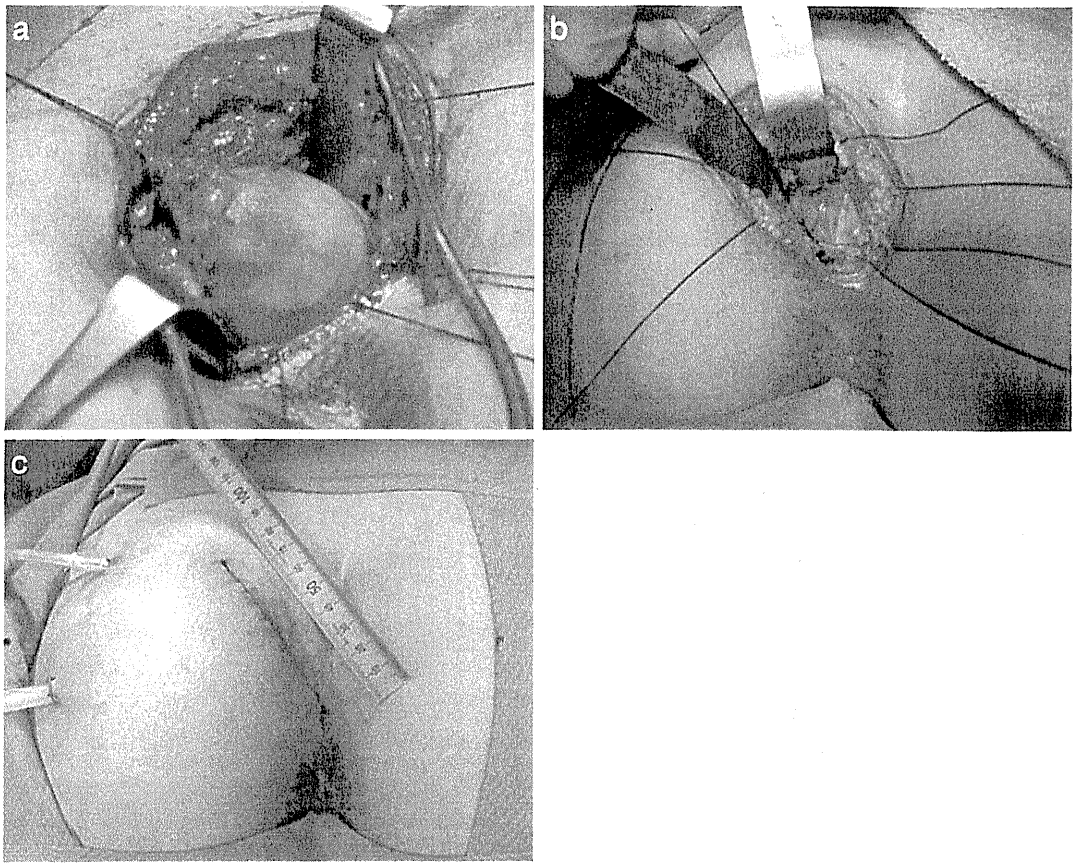

Fig. 2　症例1の術中所見
a：尾骨を切除し，術野の視野を確保した．
b：腫瘍切除後．
c：手術終了後．約7 cmの皮切で終了した．

考　察

仙骨前面と直腸後面に囲まれたpresacral spaceには胎児期にcaudal endが存在し，多数の胎児期組織が集合しており，様々な腫瘤が発生することが知られている．前仙骨部に発生する腫瘤をJackmanら[1]は，先天性，炎症性，神経原性，骨原性，その他の5つに分類している．

Hawkinsら[2]は先天性腫瘤のなかの嚢胞状腫瘤をdevelopmental cystと定義し，dermoid cyst，epidermoid cyst，mucus secreting cyst(tail gut cyst)の3つに分類し，それぞれの発生頻度を47.5%，40%，12.5%と報告している．dermoid cyst，epidermoid cystは外胚葉性成分の迷入と考えられており，dermoid cystは皮膚附属器を伴い，epidermoid cystは伴わないことから鑑別される．mucus secreting cystは胎生期のtail gutの遺残によって生じ円柱上皮で構成される．この他，teratomaが鑑別診断として挙げられるが，teratomaは2胚葉以上の成分がみられることから鑑別される．以上，developmental cystの鑑別診断はTable 1のようにまとめることができる．自験例2例は多量の角化物を伴い，嚢胞壁は重層扁平上皮から構成され，皮膚附属器をともなわないことからepidermoid cystと診断した．

医中誌Webを用いて，1983年から2010年10月までの期間で，「前仙骨部」，「presacral space」「類表皮嚢腫」，「epidermoid cyst」をキーワードにして検索したところ，本邦において74例の報告[3-8]があり，それに自験例を含めた76例について臨床病理学的検討を行った（Table 2）．年齢中央値は46歳（6歳～83歳），男女比は約1：4であり女性に多く認められた．腫瘍径中央値は75㎜（20㎜～300㎜）であり，大きさは大小様々であった．

無症状で偶発的に発見されることが多いが，自覚症状として便秘，肛門痛，下腹部痛，会陰部違和感などが報告されている[9]．本疾患の診断方法として，

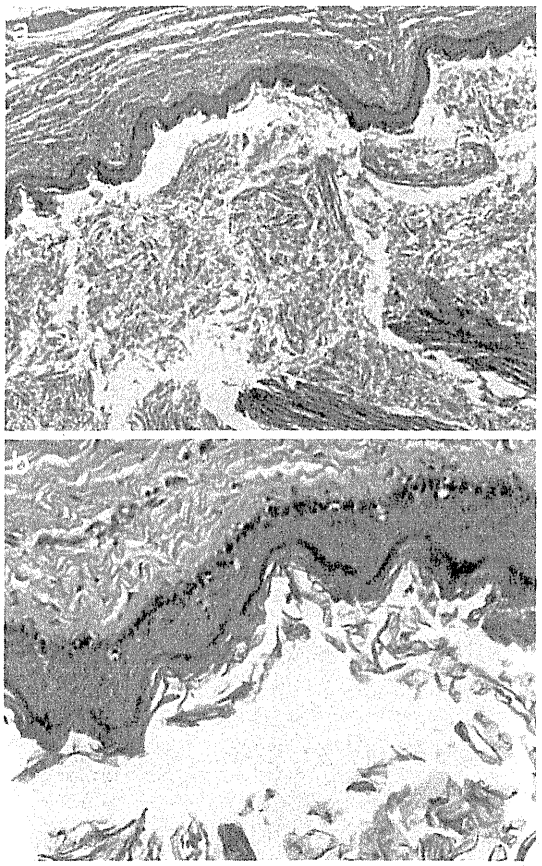

Fig. 3　症例1の病理組織所見
a：弱拡大．嚢胞内に多量の角化物を認めた．
b：強拡大．嚢胞壁に重層扁平上皮を認めたが，皮膚付属器の混在は認めなかった．

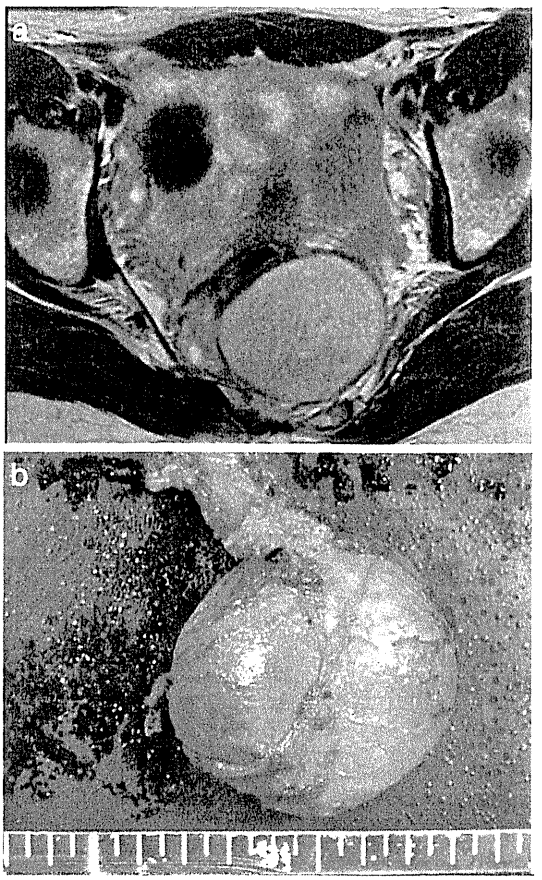

Fig. 4　症例2の検査・手術所見
a：症例2の骨盤MRI検査（T2強調画像）．直腸左後方に位置する高信号を示す内部が均一な腫瘤性病変を認めた．
b：症例2の切除標本．6.5×6.0cmの嚢胞性腫瘍．

直腸診は前仙骨部に存在する腫瘤を直接触知することができる非侵襲的かつ簡便な検査の1つである[10]．さらに，超音波検査でも腫瘍の存在を確認することができ，直腸診と超音波検査で異常を認めることを契機としてCT検査やMRI検査などの精密検査に進むことが多い．epidermoid cystはCT検査，MRI検査で造影効果のない均一な内容物を含む嚢胞性病変として描出されるが，これらの検査は腫瘍径や性状，周囲臓器との位置関係，良悪性の鑑別などの術前診断に有用である．なお良悪性の鑑別に関しては，嚢胞性腫瘍の壁肥厚や不均一な造影効果が一助となるものの，確定診断には病理組織学的診断が必須である[10-12]．

本邦において悪性例は3例（3.9%）報告されている[13-14]．このうち2例は術後早期に局所再発を認めており，術後14ヵ月以内で死亡している．epidermoid cystを含むdevelopmental cystは，海外の症例でもしばしば悪性化することが報告されている[10-12]．そのため，developmental cystの治療においては手術による完全切除が重要と認識されている．

切除術式としてこれまでに様々な方法が検討されているが，transabdominal approach，posterior approach，combined transabdominal/posterior approachの3つに大きく分けることが出来る（Table 3）[8,15]．transabdominal approachでは直腸の後方に直接腫瘍を露出することが可能であり，周囲の血管や直腸の位置関係を確認することができる．しかし，腫瘍の位置がS3より低い場合には腫瘍の露出が困難なため，S3より高い位置にある腫瘍に対して有用であり，posterior approachはS3より低い位置にある腫瘍に対して有用と考えられている[17]．Posterior approachはjack-knife positionで行い，傍仙尾切開や水平切開で皮膚切開し，肛門尾骨靭帯と肛門挙筋を分けて腫瘍を露出する．Combined approachは

Table 1　presacral cystic tumors の鑑別診断

	Origin	Skin appendages	Figuration	Content organization
Developmental cyst				
Dermoid cyst	Ectoderm	Contain	Multilocular	Gruel-like
Epidermoid cyst	Ectoderm	Do not contain	Monolocular	Gruel-like
Tail gut cyst	Retained tail gut	Do not contain	Multilocular	Mucin, Gruel-like
Teratoma	More than dipoblastic	Contain		

Table 2　本邦における presacral epidermoid cyst の報告例

	n=76
Age*	46 (6-83)
Sex (M : F)	15 : 59
Tumor size* (cm)	75 (20-300)
≦10cm	55
>10cm	16
Malignant degeneration	2
Procedure	
Transsacral approach	52
Transabdominal approach	21
Unknown	3

腹部と会陰部の両方から腫瘍を露出することにより血管と仙骨神経の温存を最大限可能とする．前仙骨部に位置する腫瘍では posterior approach のほうが病変に到達しやすいと考えられており，術後癒着による腸閉塞の危険も少なく，優位性が指摘されている．現在，欧米では presacral tumor（retrorectal tumor）の術式を選択する上で，腫瘍径が10cm以下[16]あるいは8cm以下[9,17]のものが posterior approach の適応とする報告がある．

本邦報告例の術式を検討すると，transabdominal approach と，posterior approach の1つである transsacral approach の2つが多くの例に対して選択されている．とくに transsacral approach は52例（全体の68.4%）において施行されている．また，その他の術式としては腹腔鏡補助下手術や傍肛門弧状切開などが報告されている．本邦の術式選択の指標について検討すると，腫瘍径7cm以下のもので transsacral approach が多く選択されているが，10cmを超える大きな腫瘍でも本法が選択された例があり，腫瘍径による術式の選択基準は明確でない（Table 4）．

developmental cyst は悪性の可能性があるため完全切除を基本的要件とするならば，腫瘍径による術式の選択基準を定めることは重要と考える．本症例は，2例ともに7cm以下の腫瘍であり，transsacral approach にて完全切除が可能であった．ともに若年女性であり，根治性のみならず整容性や術後の肛門・排便機能の面でも tranassacral approach が有用であった症例である．

術前の画像検査での良悪性の判断は困難であり，穿刺生検では悪性腫瘍の場合播種の可能性がある．病巣の完全切除のためには腫瘍の局在がS3より尾側にあり，腫瘍径が7cm以下の症例を transsacral approach の適応と我々は考えている．また，腫瘍内溶の漏出により再発をきたした報告例があり，この術式を行う場合には習熟した外科医の執刀あるいは助手による参加が望ましいと思われる．

予後については，完全切除が可能であった症例では再発はなく，良好であることが知られている．腫瘍径が10cmを超えるものでも，完全切除ができた症例では再発を認めていない．しかし，上村ら[3]の症例では不完全切除のため局所再発を認め，永野ら[13]の症例は悪性所見を認め，術中内容物の流出，もしくは術前の生検が原因の局所再発で術後14ヵ月で死亡している．以上より epidermoid cyst を含む developmental cyst の治療では手術による完全切除が重要であり，術式が予後に影響する可能性があるため，術式の選択は根治性と整容性，術後機能を考慮し慎重に検討すべきである．

Table 3 presacral tumors に対する手術方法の比較．文献15）の Table 2 を改変

Type of Procedure	Advantages	Disadvantages Limitations
Transabdominal	Large working space Easy for complete resection	Only for higher-lying lesion Large incision in stomach
Posterior	Low invasive Small incision Better cosmetic wound	
Transsacral	No bowel obstruction by the postoperative adhesion	Requires a coccyx resection Risk of fistula formation Risk of nervous sacral lesion Risk of poor function of defecation
Parasacrococcygeal	Good exposure Coccyx may remain in place	Only for low-lying lesions
Transanorectal	Useful in cases of ruptured transrectal cysts	Difficult for complete resection Very small working space
Transvaginal		Not frequent procedure
Transshincteric		Risk of poor function of the sphincter
Intersphincteric	Preserves a good sphincter function Uses an embryological avascular plane	Only for very low-lying lesions When there is no preoperative suspicion of malignancy
Combined	When the tumor is large and have the suspicion of malignancy	

Table 4 本邦における presacral epidermoid cysts に対する術式と腫瘍径の比較

	Transsacral (n=48)	Transabdominal (n=21)
Tumor size		
≦10cm	39	14
>10cm	9	7
≦8cm	32	10
>8cm	16	11
≦7cm	27	6
>7cm	21	15

結　語

今回われわれは，成人の前仙骨部に発生した2例の epidermoid cyst を経験した．本邦報告例を検討したが，いまだ確立した術式の選択基準はなく，今後更なる検討が必要である．

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A Report of Two Cases of Presacral Epidermoid Cyst in Adults

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Two young females in whom a pelvic mass had been found by medical check-up visited our hospital. Magnetic resonance imaging revealed 6-cm and 5-cm well-circumscribed homogeneous cysts, respectively, in the presacral region. T2 weighted images demonstrated cystic lesions with uniformly high-intensity signal. Computed tomography scans also demonstrated cystic lesions with a smooth thin wall and homogenous fluid, but not a solid structure. Therefore, we clinically diagnosed them as presacral cystic tumors, and performed complete resections by the transsacral approach with removal of coccygeal bone. In both cases, histopathological examination revealed stratified squamous epithelium but not skin appendages, so they were histopathologically diagnosed as epidermoid cysts. After surgery, anal dysfunction and tumor recurrence were not observed in either case.

The presacral space is known to be the origin of various tumors that develop from embryologic structures. Among them, developmental cysts arising from any embryonic layer are classified into three groups: dermoid cyst, epidermoid cyst, and tail gut cyst, which have a risk of malignant transformation, albeit rarely. Although complete surgical resection should be carried out for these diseases, there is no clear indication of the surgical procedure or approach. Further investigations are necessary to establish surgical indications and approaches for these diseases.

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CLINICAL INVESTIGATION **Rectum**

A PHASE II TRIAL OF NEOADJUVANT PREOPERATIVE CHEMORADIOTHERAPY WITH S-1 PLUS IRINOTECAN AND RADIATION IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER: CLINICAL FEASIBILITY AND RESPONSE RATE

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Purpose: We aimed to validate our hypothesis that a preoperative chemoradiotherapy regimen with S-1 plus irinotecan is feasible, safe, and active for the management of locally advanced rectal cancer in a single-arm Phase II setting.
Methods and Materials: Eligible patients had previously untreated, locally advanced rectal adenocarcinoma. Radiotherapy was administered in fractions of 1.8Gy/d for 25 days. S-1 was administered orally in a fixed daily dose of 80mg/m^2 on Days 1 to 5, 8 to 12, 22 to 26, and 29 to 33. Irinotecan (80mg/m^2) was infused on Days 1, 8, 22, and 29. Four or more weeks after the completion of the treatment, total mesorectal excision with lateral lymph node dissection was performed. The primary endpoint was the rate of completing treatment in terms of feasibility. The secondary endpoints were the response rate and safety.
Results: We enrolled 43 men and 24 women in the study. The number of patients who completed treatment was 58 (86.6%). Overall, 46 patients (68.7%) responded to treatment and 24 (34.7%) had a complete histopathologic response. Three patients had Grade 3 leukopenia, and another three patients had Grade 3 neutropenia. Diarrhea was the most common type of nonhematologic toxicity: 3 patients had Grade 3 diarrhea.
Conclusions: A preoperative regimen of S-1, irinotecan, and radiotherapy to the rectum was feasible, and it appeared safe and effective in this nonrandomized Phase II setting. It exhibited a low incidence of adverse events, a high rate of completion of treatment, and an extremely high rate of pathologic complete response. © 2011 Elsevier Inc.

Chemoradiation, Rectal cancer, S-1, Irinotecan.

INTRODUCTION

In Japan the incidence of colorectal cancer (CRC) is increasing year by year. If this trend continues, forecasts estimate that about 170,000 people will have CRC in 2015. Colorectal cancer will become the most prevalent type of cancer in Japan, surpassing gastric cancer and lung cancer (1). In Europe and North America, CRC is the second leading cause of cancer-related death, behind lung cancer. Globally, the prevention, early diagnosis, and treatment of CRC are urgent tasks.

Advanced rectal cancer carries a poorer prognosis than advanced colon cancer. The control of local recurrence, a unique characteristic of rectal cancer, and improved overall survival are important goals of treatment. Total mesorectal excision (TME) has recently been shown to decrease the rate of local recurrence and is performed throughout the world as a standard procedure (2, 3). In the mid 1980s the Gastrointestinal Tumor Study Group showed that postoperative chemoradiotherapy improves the rate of recurrence-free survival (4). On the basis of these results, the National Institutes of Health in the United States has recommended resection plus postoperative chemoradiotherapy as standard therapy for pathologic Stage II and III rectal cancer since 1990 (5). Five controlled studies comparing preoperative radiotherapy followed by surgery with surgery alone subsequently showed that the rate of local recurrence is significantly lower in patients who receive preoperative radiotherapy than in those who receive surgery alone (6). Moreover, the Swedish Rectal Cancer Trial showed that preoperative radiotherapy significantly improves overall and disease-free survival (7). On the other hand, European Organisation for Research and

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Treatment of Cancer Trial 22921, a large Phase III study, failed to prove that chemoradiotherapy improves survival rates, but the control of local recurrence at 5 years was significantly better in patients who received chemoradiotherapy than in those who received radiotherapy alone if chemotherapy was given at any time during the course of treatment (8). On the basis of these results, preoperative chemoradiotherapy was acknowledged to be standard treatment for locally advanced rectal cancer. However, the dose, duration, and radiation target volumes, as well as optimal concomitant agents, remain controversial. Recently, Guillem *et al.* (9) reported that patients with a complete response (CR) or nearly complete response to preoperative chemoradiotherapy have good long-term outcomes. Attention has thus focused on the relation between CR ratio (tumor downstaging) and survival outcome by preoperative chemoradiotherapy.

In Japan, however, few clinical trials of adjuvant radiotherapy have been conducted because the rate of local recurrence after the Japanese standard therapy (TME plus lateral lymph node dissection without neoadjuvant radiotherapy) is comparable to that including neoadjuvant chemoradiotherapy in Europe and North America. Because surgery alone has reached the most optimal outcome for decreasing local recurrence or improving survival of advanced rectal cancers in Japan at present, we wondered whether it is really necessary to evaluate chemotherapy combined with radiotherapy to improve clinical outcomes.

S-1 is an oral anticancer drug that combines tegafur, which is finally converted to the active agent of 5-fluorouracil (5-FU), with gimeracil and oteracil potassium. Gimeracil was added to increase the blood 5-FU concentration by inhibiting metabolism of 5-FU by dihydropyrimidine dehydrogenase mainly in the liver. On the other hand, oteracil potassium is widely distributed to gastrointestinal tissues and antagonizes orotate phosphoribosyl transferase, resulting in inhibition of 5-fluoronucleorides (active metabolites) generated from 5-FU, as well as reduced toxicity of 5-FU. Moreover, we also focused on the recently proven fact that components of S-1 markedly increase the radiosensitivity of cancer cells (even 5-FU–resistant cells) to radiotherapy in CRC (10). In addition, irinotecan hydrochloride decreases messenger ribonucleic acid levels of thymidylate synthase as a target enzyme of 5-FU (11), thereby augmenting its inhibition (12). Several studies have also shown that 5-FU induces topoisomerase I and that cancer cells overexpressing topoisomerase I increased chemosensitivity against irinotecan (13, 14). Such *in vitro* mechanisms provide a theoretic basis for combining S-1 and irinotecan plus radiation therapy (Fig. 1). At present, 5-FU–based chemoradiotherapy is used as a standard treatment for rectal cancer (4, 15); however, our 5-FU–based chemoradiotherapy was considered worthy of investigation.

A Phase I clinical study was performed to determine the maximum tolerated doses and recommended doses of S-1 and irinotecan. The pathologic response rate to the recommended dose, though not the primary endpoint in the Phase I study, however, was 94.7%, and the pathologic CR rate was surprisingly 31.6%, indicating that treatment with S-1 and irinotecan plus radiation was very active for locally advanced rectal cancer (16). In this Phase II clinical trial, we aimed to validate our hypothesis that a preoperative chemoradiotherapy regimen with S-1 plus irinotecan is feasible, safe, and effective for the management of locally advanced rectal cancer.

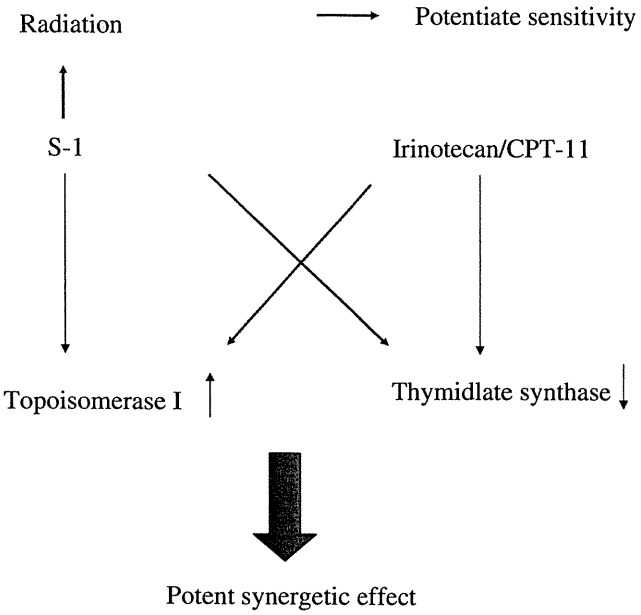

Fig. 1. Interaction of S-1 and irinotecan.

METHODS AND MATERIALS

This study was performed according to the guidelines of the Declaration of Helsinki, as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Kitasato University Hospital (Kanagawa, Japan). All patients gave written informed consent before study entry.

Eligibility criteria

Eligible patients had previously untreated clinical T3 or T4, N0 to N2, M0 locally advanced rectal cancer as confirmed histopathologically as adenocarcinoma in the rectum from August 2005 through December 2007, as well as an Eastern Cooperative Oncology Group performance status of 0 to 2. We used the International Union Against Cancer staging system. We described rectal cancer as involving the portion of the rectum above the peritoneal reflection and the portion of the rectum below the peritoneal reflection and ruled out other portions using the Japanese classification of CRC, and our definition of the rectum is thus the same as that of the International Union Against Cancer. Other eligibility criteria were as follows: age 20 to 80 years at enrollment; no severe disturbances of main organ functions (including bone marrow, heart, lung, liver, and kidney); no severe hematologic or blood chemical abnormalities such as leukocyte count of 4,000 to 12,000/mm^3, neutrophil count of 2,000/mm^3 or greater, platelet count of 100,000/μL or greater, hemoglobin concentration of 9.0 g/dL or greater, total bilirubin concentration of 1.5 mg/dL or less, serum aspartate aminotransferase and alanine aminotransferase levels less than twice the upper limit of normal, serum creatinine concentration less than the upper limit of the normal; normal electrocardiographic findings; and the ability

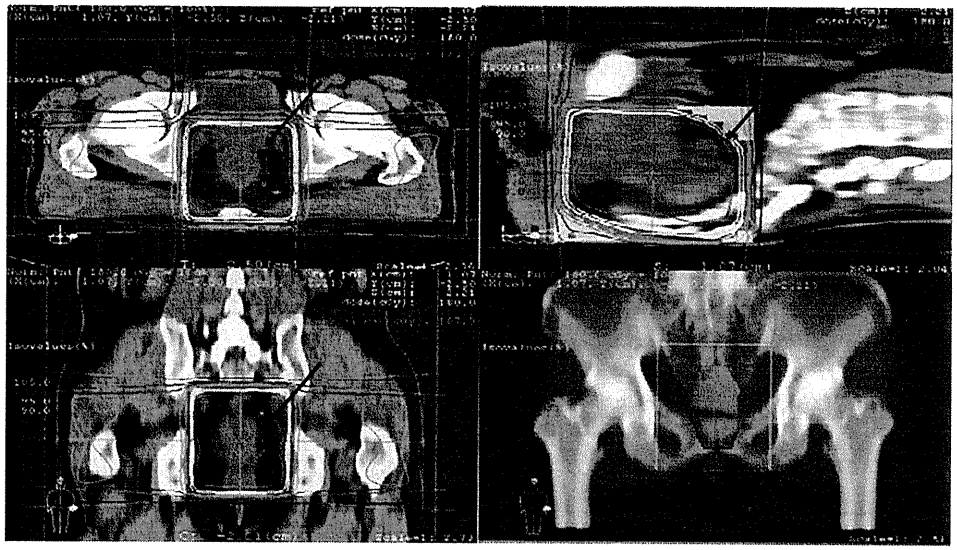

Fig. 2. Treatment field of radiation therapy.

to ingest solid foods and drugs orally. The eligible patients could not be transfused with red cells to meet these criteria.

Before enrollment in the study, we reviewed the histories of past and present disease and the general condition of all patients, assessed based on interview, physical examination, and blood tests. Locally advanced rectal cancer (clinical T3 or T4) without distant metastasis was confirmed by barium enema; colonoscopy including histopathologic evaluation; computed tomographic scans of the chest, abdomen, and pelvis; and magnetic resonance imaging (MRI) of the pelvis. Magnetic resonance imaging of the pelvis is useful to differentiate the clinical diagnosis of T3 and T4 and lymph node metastasis adjacent to the rectum. Differential diagnostic standards of MRI dictate that clinical T3 indicates a breach of the outer layer of the longitudinal muscle on T2 intensity imaging and T4 indicates irregular invasion to the extracorporeal region of the rectum on T1 intensity imaging.

Radiotherapy and chemotherapy

The treatment field of radiotherapy has been published previously (16). In brief, radiotherapy was administered in fractions of 1.8 Gy/d, given 5 days per week for 5 weeks. The total dose of radiation was 45 Gy. Patients were treated in the prone position, by use of a dedicated device (lead board) to minimize exposure of the small bowel. A computed tomography–based treatment planning system was mandatory to define the planned target volume (PTV), which allowed for setup error, organ movement, and a 1-cm circumference (clinical target volume) around both the primary tumors including regions invading surrounding organs or tissues and the adjacent swollen lymph nodes (gross tumor volume) (Fig. 2). The PTV was treated with radiation from a 10-MV linear accelerator, and we used a four-field box technique. The clinical target volume for the primary tumor used in this study typically included the perirectal lymph nodes. The target volumes used for radiotherapy in this study are far smaller in comparison to those usually described in North American and European practice, where the internal iliac nodes and often the external iliac nodes are electively irradiated. Thirty-eight patients had swollen lymph nodes included in the gross tumor volume preoperatively, and none was outside the PTV for radiotherapy. The response rate of the primary tumor was graded, but that of lymph nodes was not assessed.

S-1 (80 mg · m^{-2} · d^{-1}) was given orally after breakfast and dinner on Days 1 to 5, 8 to 12, 22 to 26, and 29 to 33. Irinotecan (80 mg · m^{-2} · d^{-1}) was given as an intravenous infusion over a period of 90 minutes on Days 1, 8, 22, and 29. The relative dose of irinotecan between the folinic acid, 5-FU, and irinotecan regimen and that used in this study is 180 mg/m^2 biweekly vs. 80 mg/m^2 weekly (180/160 = 1.125). The rationale for using a 1-week interval for chemoradiotherapy was to allow recovery of the patient's fatigue. It was our impression that a shorter interval duration would lead to several patients discontinuing the regimen before its completion.

Surgery

Total mesorectal excision with bilateral autonomic nerve preservation was performed, and lymph nodes were dissected from the middle rectal, internal iliac, and obturator lymph node regions. For sphincter-preserving surgery, the anorectal side of the rectum was divided, leaving a margin of at least 2 cm from the inferior border of the tumor. Abdominoperineal resection was done if the distal margin was insufficient.

Criteria for modification of treatment schedule and dosage

Our protocol specified that the regimens may be suspended for Grade 3 or worse diarrhea and nausea/vomiting, and we prospectively assessed hematologic, urinary, and dermatologic toxicities every 7 days by blood, urine, and dermatologic assessment. Toxicities were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 2. If toxicity necessitated a dose reduction within a course of treatment, the dose could be decreased by one step (20%) of irinotecan and treatment resumed. If toxicity requiring a further dose reduction recurred after the dose was decreased by one step, the study was terminated in the patient, with no further decrease in dosage.

Method for calculating rate of completing treatment

The ratios of the total administered dose to the total scheduled dose up to the date of surgery were calculated for radiotherapy,

S-1, and irinotecan by the following formula: Administered dose/Scheduled dose × 100 (%). We defined completing treatment as administered dose equal to or over 75% of full dose, and such cases actually coincided with the patients who were given 100% of the dose of chemotherapy.

Method for calculating rate of response

After surgery, the responses of tumors to chemoradiotherapy were histopathologically evaluated by examining serial sections of the resected specimens. Responses were evaluated based on the degree of degeneration or necrosis and fusion of cancer cells. No response was assigned a grade of 0, and a CR was assigned a grade of 3. The criteria for histopathologically evaluating the response to preoperative chemoradiotherapy, according to the Histopathological Response Criteria of the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus edited by the Japanese Society for Cancer of the Colon and Rectum, have been previously described (16). In brief, complete, considerable, and slight responses coincide with Grade 3, Grade 2, and Grade 1, respectively.

Endpoints and statistical considerations

The primary endpoint was the rate of completing treatment in terms of feasibility. The secondary endpoints were the response rate, safety (incidences of adverse reactions and complications), local recurrence rate, and overall survival. The response rate is determined based on pathologic CR, as well as incidences of adverse reactions including hematologic, urologic, dermatologic, and symptomatic complications. Data on local recurrence and overall survival are not presented in this report, because follow-up is not sufficient to allow conclusions regarding survival outcome.

We calculated the required sample size for this study based on a target rate of treatment completion of 70% and a minimum completion rate of 50%, with an α error of 0.05 (1-sided) and a β error of 0.1. The required number of patients was estimated to be 50. In anticipation of 10% of patients being ineligible, we planned to enroll 55 patients. Ineligible patients were those who did not provide informed consent or who had rectal cancer located in portions other than those above the peritoneal reflection or below the peritoneal reflection. Patient enrollment was discontinued at the end of the month when the target number of 55 subjects had been reached. The final number of enrolled patients was 67. The final number was higher than the target number of 55 by 12, but less than 1 month had elapsed between the dates of enrollment of Patient 55 and Patient 67. Moreover, Patient 67 started treatment before the results for Patient 55 were analyzed. We therefore decided that the histopathologic findings from all enrolled patients should be included in this analysis and considered this a valid procedure. The final number of enrolled patients was therefore higher than the initially planned target number.

RESULTS

Table 1 shows the demographic characteristics of the 67 patients with locally advanced rectal cancer who were eligible for the study and received preoperative chemoradiotherapy at our hospital. Median follow-up was 26 months (range, 11 to 51 months).

Table 1. Clinical characteristics of patients with locally advanced rectal cancer who received preoperative chemoradiotherapy

Clinical characteristic	Data	%
Sex		
Male	43	64.2
Female	24	35.8
Age (y)		
Median	63	
Range	32–79	
ECOG performance status		
0	67	100
1	0	0
Tumor site		
Ra	23	34.3
Rab	7	10.5
Rb	37	55.2
Depth of invasion		
T3	56	83.6
T4	11	16.4
Preoperative chemoradiotherapy		
Lymph nodes		
N0	30	44.8
N1	36	53.7
N2	1	1.5

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ra = rectum above peritoneal reflection; Rab = rectum above and below peritoneal reflection; Rb = rectum below peritoneal reflection.

Data are presented as No. of patients, unless otherwise indicated.

Primary endpoint

Of the 67 patients, 66 (98.5%) completed treatment based on our definition of completing treatment. The dose of irinotecan was reduced by 20%, and the radiation and S-1 protocols were not changed (except in 1 patient, who forgot to take S-1 for several days and in whom final S-1 compliance was equal to or over 90% but less than 100%, as shown in Table 2). Eight patients exhibited irinotecan compliance equal to or over 70% but less than 80% (Table 2). Finally, 1 patient who did not complete treatment had Grade 3 anorexia, nausea, and vomiting, and these symptoms responded to treatment with fluid therapy; however, treatment was discontinued at the patient's request. On the other hand, the rate of completing treatment reached 86.6% (58 of 67) per the protocol according to the criteria of the Cancer and Leukemia Group B (CALGB) study (17), where rates of completing treatment were determined in two categories of patients—those having completed six cycles of oxaliplatin (56%) and those having completed at least four cycles of therapy (72%). In our study 58 patients completed treatment with 100% of the dosage (including four cycles of chemotherapy).

Secondary endpoints

The pathologic response was Grade 3 (pathologic CR in the primary cancer) in 25 (37.3%) of 67 patients (Table 3). Because we included 1 case with lymph node metastasis, the number of bona fide cases exhibiting pathologic CR was therefore 24 patients (34.7% [24 of 67]) (Table 4). The

Table 2. Treatment exposure

Relative dose intensity (%)	S-1* (median dose intensity, 80 mg · m^{-2} · d^{-1} × 25 days)		Irinotecan (median dose intensity, 80 mg · m^{-2} · d^{-1} × 4 days)	
	No. of patients	%	No. of patients	%
100	65	97	58	86.6
≥90 to <100	1	1.5	0	0
≥80 to <90	0	0	0	0
≥70 to <80	0	0	8	11.9
Missing	1	1.5	1	1.5

* The maximum dose of S-1 was 120 mg · m^{-2} · d^{-1}.

rate of pathologic CR was 31.6% in the Phase I setting (16), and our result was comparable in this Phase II setting. The total response rate involving both Grade 2 (considerable response) and Grade 3 (CR) was 68.7% (46 of 67 patients), whereas that including even Grade 1a/1b (slight response) reached 100%, if evaluated in the primary cancers (Table 3). Although no cancer cells were found in 54 patients (80.6%) on colonoscopy with biopsy after chemoradiotherapy, more than half of these patients were actually confirmed to have residual disease on histopathologic examination of the resected specimens.

Safety includes incidences of adverse reactions and complications, and adverse events as acute toxicities are summarized in Table 5. Adverse events are infrequent, and there was no Grade 4 hematologic or nonhematologic toxicity. Regarding hematologic toxicity, only 3 patients had Grade 3 leukopenia and 3 had Grade 3 neutropenia. One patient with Grade 3 leukopenia concurrently had Grade 3 thrombocytopenia. Regarding nonhematologic toxicity, only 3 patients had Grade 3 diarrhea, which promptly improved after treatment with a continuous intravenous infusion. One patient had Grade 3 anorexia and nausea; treatment was withdrawn before completion at the patient's request. Activity of either dihydropyrimidine dehydrogenase or orotate phosphoribosyl transferase enzyme was not assessed in this study, but such enzyme deficiency might have been involved in the patient with Grade 3 anorexia and nausea.

Surgical procedures and pathologic findings

Of the 67 patients, 50 (74.6%) underwent sphincter-preserving surgery and 17 (25.4%) underwent abdominoperineal resection. A diverting ileostomy was created in all patients who underwent sphincter-preserving surgery. We currently perform ileostomy for patients who had sphincter-preserving surgery in case of anastomotic leakage, because we are afraid that the low anterior resection was done after radiation therapy. Such ileostomy is a transient stoma and usually reversed 6 months to a 1 year later. For patients undergoing abdominoperineal resection, the sigmoid colon was diverted.

The median number of examined lymph nodes was 19 (range, 12 to 52). Among the 67 patients, 26 were found to have lymph node metastasis: 18 (26.9%) had pathologic N1 disease (1–3 metastatic regional lymph nodes) and 8 (11.9%) had pathologic N2 disease (≥4 metastatic regional lymph nodes). The relation between the response of the primary tumor and lymph node metastasis is shown in Table 4. Downstaging of the primary tumor according to clinical T stage was confirmed in 49 patients (73.1%). Of the 37 patients evaluated to have node-positive disease before treatment, 16 (43.2%) had no pathologic evidence of lymph node metastasis. In 1 patient with a Grade 3 response of the primary tumor, 2 metastatic lymph nodes were found in the field of the inferior mesenteric artery.

In 6 of the 26 patients with lymph node metastasis, metastatic lymph nodes along the internal iliac artery and obturator foramen were recognized but were dissected by surgery. These patients all had enlarged lymph nodes in these regions on computed tomography and/or MRI before treatment. Such patients with pathologic evidence of lymph node metastasis also received six courses of postoperative adjuvant chemotherapy with S-1 (80 mg/m^2), given for 14 days, followed by 14 days of rest, and irinotecan (125 mg/m^2), given on Days 1 and 15.

Table 3. Pathologic primary tumor response as secondary endpoint

Grade	Response to treatment	
	No. of patients	%
1a	5	7.5
1b	16	23.9
2	21	31.3
3	25	37.3

The response rate was good in 68.7% of patients, and the response rate was good or slight in 100%.

Table 4. Relation between response to treatment and lymph node metastasis

Grade	Response to treatment		
	No. of patients	No. of patients with lymph node metastasis	%
1a	5	1	20
1b	16	12	75
2	21	12	57.1
3	25	1	4

Table 5. Acute toxicity during treatment course

	Grade 1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Hematologic toxicity				
Leukopenia	0	10 (14.9)	3* (4.5)	0
Neutropenia	0	1 (1.5)	3 (4.5)	0
Thrombocytopenia	0	0	1* (1.5)	0
Nonhematologic toxicity				
Diarrhea	2 (3.0)	2 (3.0)	3 (4.5)	0
Anorexia/nausea	0	0	1 (1.5)	0

* One patient had leukopenia and thrombocytopenia.

Postoperative complications

Postoperative bleeding from a branch of the internal iliac vein required emergency surgery to achieve hemostasis. One patient with intestinal obstruction did not respond to conservative treatment and underwent reoperation (untethering). There were no perioperative or postoperative deaths or postoperative sequelae.

DISCUSSION

Our protocol is considered sufficiently safe, with high rates (86.6%) of completing treatment as compared with the previous studies. There was no Grade 4 toxicity, and all Grade 3 adverse events responded to conservative treatment. In the European Organisation for Research and Treatment of Cancer 22921 study, the rate of completing treatment was 82.0% in the two groups who received preoperative chemoradiotherapy (6). In the CALGB 89901 study, the incidence of Grade 3 or 4 diarrhea was 38% in patients who received preoperative chemotherapy with oxaliplatin plus 5-FU, and the percentage of patients who completed treatment was 72% (17), if we consider completing treatment to have been achieved with at least four cycles of therapy, similar to the definition we used. The recommended dose determined based on a Phase I clinical study of our regimen was thus deemed to be appropriate (16).

The low incidence of complications might be attributed primarily to the fact that the irradiated field was adequately reduced. The target volumes used for radiotherapy in this study are far smaller in comparison to those usually described in North American and European practice, where the internal iliac nodes and often the external iliac nodes are electively irradiated. We have to keep this difference in mind in determining whether we can safely use S-1 and irinotecan along with the more typical larger radiotherapy volumes used compared with the volumes used in this study. Reduced irradiated fields of our protocol can be reasoned for surgical procedures including lateral lymph node dissection, which is one of the standard surgical options in Japan.

The rate of pathologic CR in our study was 34.7%, which was clearly higher than the rates (11%–17%) in the previous studies (8, 18–21) (Table E1). In our study serial sections of tumor tissue were evaluated histopathologically. The reliability of the pathologic evaluation of CR is therefore considered higher than that in previous studies. The median number of dissected lymph nodes was 19 (range, 12–52), considered adequate for lymph node dissection. The addition of another anticancer agent to 5-FU–based chemotherapy plus radiotherapy at a dose of 45 Gy or higher was found to contribute to a higher rate of pathologic CR, consistent with the results of other studies (22, 23). The rate of pathologic CR to 5-FU/leucovorin regimens was 20% or less in most studies. In the CALGB 89901 study, in which patients also received oxaliplatin, the rate of pathologic CR improved to 25%, but serious diarrhea and a low rate of completing treatment were problems (17). With our regimen for chemoradiotherapy, the rates of completing treatment (86.6%) and of pathologic CR (34.7%) reached satisfactory levels. Such good outcomes might be attributed to increased radiosensitivity of tumor cells induced by components of S-1 or to synergism between irinotecan and tegafur (Fig. 1). UGT1A1 nucleotide polymorphisms, which are supposed to determine the sensitivity of irinotecan, were not assessed in our study. However, treatment could be completed safely, perhaps because the dose of irinotecan was lower than that used in folinic acid, 5-FU, and irinotecan regimens (88.9%).

Several retrospective studies have reported on the close association between the rate of pathologic CR and long-term outcomes (24, 25), but such a positive correlation between these factors has yet to be clearly shown in a prospective study. In our study overall survival is being followed up as a secondary endpoint. In addition to long-term outcomes, the relation between pathologic CR and the long-term outcome is an interesting issue. Some patients with a pathologic CR may have not required surgery, but postoperative histopathologic examinations are currently required to establish the occurrence of a pathologic CR. More than half of these patients with no cancer cells on colonoscopy with biopsy after chemoradiotherapy were actually confirmed to have residual disease on histopathologic examination of the resected specimens. It is therefore difficult to evaluate the bona fide response rate only on biopsy without surgery. New examination methods other than biopsy will hopefully be established to accurately evaluate pathologic CR before surgery.

Roels *et al.* (26) reported that the rates of recurrence in the pelvic cavity were 49% in the posterior region (presacral region), 21% in the lateral region (internal iliac lymph node region), and 12% in the inferior region (perineal region). Posterior and inferior lymph nodes can be adequately

removed by TME, whereas lateral lymph nodes were not included in the irradiated field in our study and were resected surgically. If these lateral lymph nodes had not been dissected, pelvic recurrence may have occurred. The irradiated field is thus expected to become an important issue in patients with enlarged lateral lymph nodes before treatment. The clinical significance of conventional lateral lymph node dissection has yet to be shown in clinical studies. To determine the optimal irradiated field for patients with lateral lymph node metastasis, we are now closely following local recurrence and outcomes, two other secondary endpoints of this study.

In conclusion, the regimen that we developed for preoperative treatment generated promising results. However, many issues remain unresolved, including the dose (including chemotherapy cycles), duration of chemoradiotherapy, radiation target volumes in patients with lateral lymph node metastasis, optimal concomitant agents, preoperative evaluation methods for response, role of adjuvant chemotherapy, and especially, survival benefit. To assess our regimen for locally advanced rectal adenocarcinoma, the durations of disease-/recurrence-free survival and overall survival should be carefully analyzed prospectively in Phase II trials, and then large Phase III trials might be anticipated.

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特集 ……下部直腸がん手術：術前化学放射線療法と肛門機能……

術前化学放射線療法で局所・骨盤内再発は0%にできるか？

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Could We do the 0% Rate of Local Recurrence in Patients who Responded to Preoperative Chemoradiation Therapy?: Satoh T[*1], Naitoh M[*1], Ikeda A[*1], Ogura N[*1], Nakamura T[*1], Onozato K[*1], Miura H[*1], Tsutsui A[*1] and Watanabe M[*1] ([*1]Department of Surgery, Kitasato University, School of Medicine)

Objects & Subjects: We conducted phase I / II studies of chemoradiotherapy with S-1 and irinotecan in patients with locally advanced rectal cancer. The study group comprised 76 patients with locally advanced rectal cancer (T3 or T4, any N) who were enrolled in phase I / II studies of preoperative chemoradiotherapy with S-1 and irinotecan, given in the recommended (irinotecan, 80 mg/m^2; S-1, 80 mg/m^2) or lower doses. **Result**: The rate of local recurrence was extremely low (0%) in our patients who responded to preoperative therapy.

Key words: Local advanced rectal cancer, Preoperative chemoradiation therapy, S-1, CPT-11
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はじめに

わが国では大腸癌の罹患率は年々増加している．このまま罹患率の増加が続けば，2015年には，大腸癌（結腸癌＋直腸癌）患者は約17万人におよび，胃癌，肺癌を抜いて第1位となると予測されている[1]．欧米先進国においても大腸癌は肺癌についで癌による死因の第2位を占めており，世界的にみても大腸癌の予防・早期診断・治療法の開発は非常に重要な課題である．

進行直腸癌は進行結腸癌に比べて予後不良であり，治療では，全生存率の向上のみならず，独特の再発形式である局所再発のコントロールが重要な課題である．近年，全直腸間膜切除術（以下TME）は局所再発率の低下をもたらし，この方法は全世界で標準治療として受けられている．さらに，術後化学放射線療法が無再発生存率を向上させたGITSG 7175[2]の結果をから，米国のNIHはp-stage IIおよび・の直腸癌の標準治療として「切除＋術後化学放射線療法」を1990年から推奨している[3]．一方，その後に行われた術前放射線単独療法と手術単独との5つの比較試験では，術前放射線治療群の局所再発率が，手術単独群より明らかに低下した[4]．さらにSwedish Rectal Cancer Trial[5]では術前放射線療法の有意なsurvival benefitが証明された．一方，大規模第・相試験であるEORTC22921試験は，化学療法併用の生存率向上を証明できなかった．しかし，その研究では，5年局所再発の制御は化学療法併用群が放射線療法単独群に比べ有意に優れて

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おり，5-FUベースの化学療法併用の意義が明らかになった[6]．これにより，術前の化学放射線療法が局所進行直腸癌の標準的治療として認められるにいたった．ただし放射線療法の線量，期間，照射範囲，および，併用薬剤の選択については一定の見解は得られていない．最近，Guillemらは術前化学放射線療法でCRまたはCRに近い効果の得られた症例の予後が良いことを報告し[7]，術前化学放射線療法によるDown Stagingと予後との相関も注目されている．

欧米が術前化学放射線療法＋TMEを標準化した一方で，わが国はTMEに側方リンパ節郭清の局所再発率が欧米と同等であったため，補助放射線療法の大規模な臨床試験はほとんど行われなかった．このような状況でわれわれは，手術単独では局所再発のさらなる低下や生存率向上は望めず，化学，放射線療法の併用を検討する必要があると考えた．

そこで，テガフール・ギメラシル・オテラシルカリウム配合剤（S-1）のギメラシルが，癌の放射線感受性を著しく上昇させること[8]，塩酸イリノテカン（CPT-11）がTSmRNA量を低下[9]させてTS阻害時間を延長[10]することに注目した．また，5-FUはTopo-Iを誘導し，TSとTopo-Iは正の相関を示すことも知られていた[11,12]．TSを阻害する5Fu系抗癌剤とTopo-I活性を阻害するCPT-11は作用機序が全く異なり，S-1とCPT-11の併用は理にかなっていると考えた．現在5-FUをベースとした化学放射線療法が標準治療とされており[3,13]，放射線療法とS-1，CPT-11の併用は理想的な組み合わせの化学放射線療法と考えた．臨床第I相試験では，S-1とCPT-11の最大耐用量（MTD: maximum tolerated dose），および，推奨用量（RD: recommended dose）を決定し，病理学的奏効率を評価した．この結果，推奨容量内での奏効率が94.7%，pCR率が31.6%であり，治療効果がきわめて高いことが判明した[14]．さらに，Primary endpointを治療完遂率，Secondary endpointsを奏効率，安全性，局所再発率，全生存期間とした臨床第・相試験を行った[15]．本稿では，中期予後を解析して，骨盤内再発を0%にできるかを検証した．

1 適格基準

組織学的検査が施行された，T3′, T4′, N0-3′の局所進行直腸癌患者のうち，Eastern Cooperative Oncology Group（以下ECOG）Performance Status0-2の症例を対象とした．また，登録時年齢が20歳以上80歳以下で，前治療（放射線療法，化学療法，ホルモン療法など）が実施されておらず，主要臓器機能（骨髄，心，肺，肝，腎など）に高度の障害がないものに対象症例を限定した．

2 プロトコール

放射線照射は，直腸周囲1 cmに1.8 Gy/day，25日間分割照射とした（図1）．S-1は，80 mg/m^2/day5日投与2日休薬で第1～5，8～12，22～26，29～33日目に経口投与する．CPT-11は第1, 8, 22, 29日目に静脈内投与した．CPT-11の投与量は，Phase Iで得られたCPT-11 80 mg/m^2（Phase I症例では，40・60・70・80 mg/m^{2}を含む）投与とした（図2）．

3 対　象

術前化学放射線療法第I・II相試験にエントリーし，推奨容量（CPT-11 80 mg/m^2，S-1 80 mg/m^2）以下で治療が行われた76症例を対象とした．

3 手　術

手術はTMEおよび両側自律神経温存しつつ両側側方リンパ節，すなわち，中直腸根リンパ節，内腸骨根リンパ節，閉鎖リンパ節のサンプリングを行った．括約筋温存手術の直腸肛門側の切離は，腫瘍下端から最低2 cm以上の切除距離を保ち施行し，肛門側縁が十分にとれない場合は　腹会陰式直腸切断術とした．

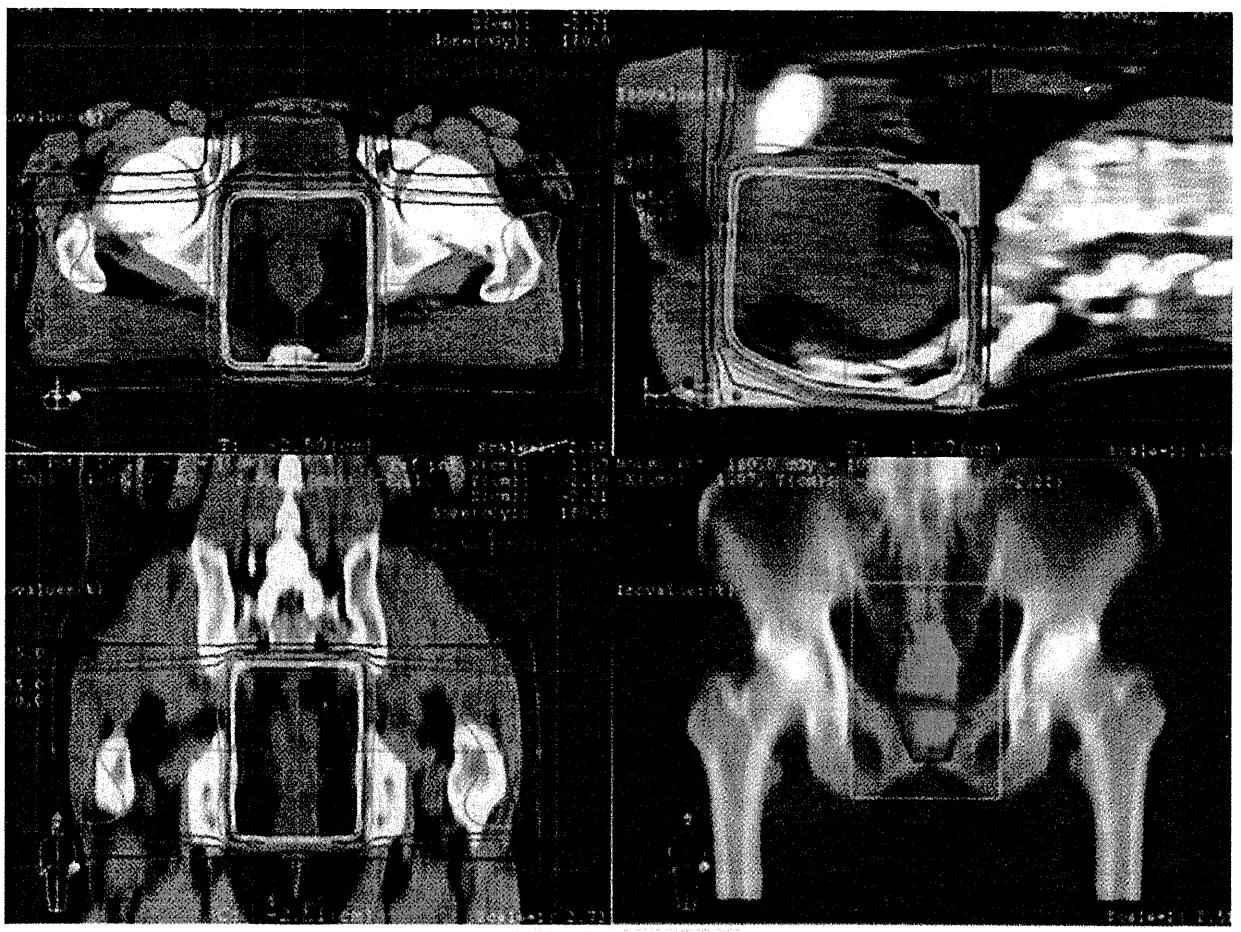

図1　放射線照射野

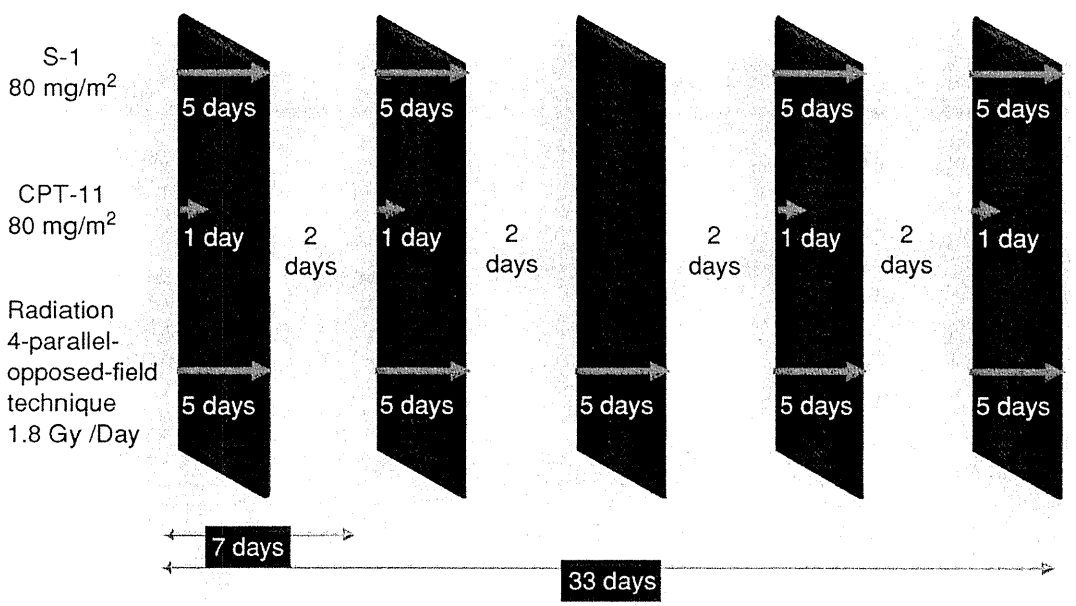

図2　試験プロトコール

4 結　果

1 Phase Ⅰ

放射線照射線量およびS-1 80 mg/m² は固定として，CPT11 40 mg/m² を投与開始量とした．CPT11 90 mg/m² が最大の最大耐用量（MTD; maximum tolerated dose）で，CPT11 80 mg/m² が推奨用量（RD; recommended dose）となった．RD以下の15症例において，術後病理学結果で，pCRは6症例で認められ，病理学的部分奏効9例であり，奏効率は100%，pCR率は40%であった．

2 Phase Ⅱ

67症例中66症例（98.5%）で治療を完遂した．治療非完遂の1症例は，食欲不振・嘔気・嘔吐Grade 3を認め，点滴加療で症状の改善は得たが，本人の希望で治療中止となった．血液毒性，非血液毒性共にGrade 4の有害事象は認めなかった．血液毒性において，Grade 3白血球減少を3例，好中球減少を3例に認めた．白血球減少の1例は，Grade 3の血小板減少も随伴した．非血液毒性ではGrade 3の下痢が3例認められたが，静脈内点滴投与で速やかに軽快した．

病理学的結果は，Grade 3（pCR）は25症例（37.3%），Grade 2は21症例（31.3%）で認められ，奏効率は68.7%であった．

術後合併症は，重篤な合併症および，死亡例は認めなかった．

3 Phase Ⅰ/Ⅱ（Phase Ⅰ 80 mg/m² 症例は，Phase Ⅱに含まれる）

観察期間中央値は4.0年で，遠隔転移再発症例数は15例（19.7%）であった．Grade別の再発率は，Grade Ⅰは11/21（52.4%），Ⅱは3/25（12%），Ⅲは1/30（3.3%）であった（表1）．再発臓器は，肝臓，肺が多く，続いて大動脈リンパ節転移であった（表2）．本臨床試験では，Gradeに関係なく，局所・骨盤内再発は認めなかった．術後長期合併症は，1例に難治性瘻孔を認め，人工肛門の再造設を要した（表3）．また，

表1　治療効果と再発

	Response n=76	Recurrence n=15
grade	n(%)	n(%)
1	21(27.6)	11(52.4)
2	25(32.9)	3(12.0)
3	30(39.5)	1(3.3)

Median Follow Up　4 yrs

表2　再発臓器

	n(%)
肝臓	6(7.9)
肺	6(7.9)
大動脈周囲	2(2.6)
全身	1(1.3)
局所・骨盤内	0(0)
計	15(19.7)

Median Follow Up　4 yrs

表3　化学放射線療法に起因する長期合併症

	n(%)
難治性瘻孔	1(1.3)
排尿機能	0(0)
男性機能（評価可能症例のみ）	0(0)
Total	1(1.3)

Median Follow Up　4 yrs

表4　死亡症例

	n(%)
Cancer rerated Death	2(2.6)
Another cause Death	1(1.3)

(RD>, n=76)　Median Follow Up　4 yrs

現病死した症例は2例（2.6%）で，1例（1.3%）で他病死を認めた（表4）．

5 まとめ

今までの化学放射線療法により局所再発率の低下に関する報告は種々散見される．しかし，骨盤内再発が0%の報告はない．本法は，pCR率がきわめて高い新しい治療法であることは報告してきた．本試験Phase ⅡのSecondary endpointで

ある全生存期間は今後の長期予後で判断できるであろう．観察期間中央値はまだ4年と短いが，比較的治療効果の低いGrade I症例でも局所・骨盤内再発は認めておらず，本法は，局所制御能が極めて高い治療法と考えられ，局所・骨盤内再発を0%にする可能性がある．S-1とCPT-11を用いた化学放射線療法は治療効果が高く，大変安全な治療である．

おわりに

われわれの研究では，治療完遂率，短期予後および，pCR率，骨盤内再発率は今までの化学放射線療法を凌駕する有望な結果を得た．今後，さらなる検討を加える必要がある．

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SPECIAL ARTICLE

Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer

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Abstract Colorectal cancer is a major cause of death in Japan, where it accounts for the largest number of deaths from malignant neoplasms in women and the third largest number in men. Many new treatment methods have been developed over the last few decades. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer (JSCCR Guidelines 2010) have been prepared to show standard treatment strategies for colorectal cancer, to eliminate disparities among institutions in terms of treatment, to eliminate unnecessary treatment and insufficient treatment, and to deepen mutual understanding between health-care professionals and patients by making these Guidelines available to the general public. These Guidelines have been prepared by consensuses reached by the JSCCR Guideline Committee, based on a careful review of the evidence retrieved by literature searches and in view of the medical health insurance system and actual clinical practice settings in Japan. Therefore, these Guidelines can be used as a tool for treating colorectal cancer in actual clinical practice settings. More specifically, they can be used as a guide to

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obtaining informed consent from patients and choosing the method of treatment for each patient. As a result of the discussions held by the Guideline Committee, controversial issues were selected as Clinical Questions, and recommendations were made. Each recommendation is accompanied by a classification of the evidence and a classification of recommendation categories based on the consensus reached by the Guideline Committee members. Here we present the English version of the JSCCR Guidelines 2010.

Keywords Colorectal cancer · Guideline · Treatment · Surgery · Chemotherapy · Endoscopy · Radiotherapy · Palliative care · Surveillance

Introduction

1. Guideline objectives

Mortality and morbidity from colorectal cancer have substantially increased in Japan recently. According to the vital statistics for Japan in 2008, colorectal cancer accounted for the largest number of deaths from malignant neoplasms in women and the third largest number in men, after lung cancer and gastric cancer. Nevertheless, the number of deaths from colorectal cancer per unit population has increased approximately tenfold during the past 50 years. Many new treatment methods have been developed during that time, and their use in combination with advances in diagnostic methods has led to a steady improvement in the results of treatment. However, there are differences in treatment among medical institutions in Japan that provide medical care for patients with colorectal cancer, and these differences may lead to differences in the results of treatment.

Under such circumstances, the JSCCR guidelines 2010 for the treatment of colorectal cancer (JSCCR Guidelines 2010), which are intended for doctors (general practitioners and specialists) who provide medical care for patients with colorectal cancer at various disease stages and conditions, have been prepared for the following purposes: (1) to show standard treatment strategies for colorectal cancer; (2) to eliminate disparities among institutions in terms of treatment; (3) to eliminate unnecessary treatment and insufficient treatment; and (4) to deepen mutual understanding between health-care professionals and patients by making these Guidelines available to the general public [1].

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