厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
肛門扁平上皮癌に対する新規化学放射線療法の確立

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研究要旨
術前化学放射線療法の効果予測因子の同定のため、局所進行直腸癌 50 症例の切除標本を用いて感受性マーカーの免疫組織化学法を行い、これらの発現と組織学的治療効果との関連を調べた。感受性マーカーとしては、腫瘍増殖関連因子や cell cycle 関連因子、apoptosis 関連因子、腫瘍間質関連因子、cancer stem cell 関連因子から計 12 種類を選出した。また、切除標本の病理組織における術前化学放射線療法の効果判定に従って、直腸癌 50 症例を high-sensitive 群と low-sensitive 群の 2 群に分類した。感受性マーカーのうち CD133 と CD24 の発現が 2 群間で有意差を認めた。また、cancer stem cell 関連因子に関して、CD133、CD24 が共に陽性の症例では low-sensitive 群が多く、共に陰性の症例では high-sensitive 群が多かった。cancer stem cell 関連因子である CD133 と CD24 の発現が局所進行直腸癌に対する術前化学放射線療法の感受性に関与すると考えられた。

A．研究目的

肛門管癌および直腸癌に対する標準治療として術前化学放射線療法が選択されている。近年本邦においても局所進行直腸癌に対する術前化学放射線療法が盛んに行われるようになっており、その有効性に関する報告も増えている。しかし、術前化学放射線療法は全症例に奏功するわけではなく有害事象も少なくないのが現状である。そのため術前化学放射線療法の適応患者を選択するために治療の感受性を予測することが必要であるが、これまでの研究報告では臨床応用可能な感受性予測因子の同定には至っていない。そこで本研究では、術前化学放射線療法の効果予測因子の同定に向けて、切除標本を用いて感受性マーカーの発現と治療効果との関係を調べた。

B．研究方法

1999 年～2010 年に当科及び関連施設において術前化学放射線療法を施行した局所進行直腸癌 50 症例を対象とした。切除標本の病理組織における術前化学放射線療法の効果判定（大腸癌取り扱い規約判定基準）に従って、Grade 3,2,1b の症例を high-sensitive 群、Grade 1a,0 の症例を low-sensitive 群の 2 群に分類した。上記 50 症例の切除標本組織に対して下記 12 の感受性マーカーの免疫組織化学を行い、これらの発現と組織学的治療効果との関連を調べた。

感受性マーカー：＜腫瘍増殖関連因子＞HER2(Human Epidermal Growth Factor Receptor Type 2)、EGFR(Epidermal Growth Factor Receptor)、＜cell cycle 関連因子＞p53、p21、Ki-67 protein、Bcl-1、＜apoptosis 関連因子＞Bcl-2、APAF-1(apoptosis protease-activating foctor-1)、＜腫瘍間質関連因子＞VEGF(Vascular Endothelial Growth Factor)、MIF(Macrophage migration Inhibitory Factor)、＜cancer stem cell 関連因子＞CD133、CD24

C．研究結果

50 症例のうち high-sensitive 群は 31 例、low-sensitive 群は 19 例であった。上記 12 の感受性マーカーのうち CD133 と CD24 の発現が 2 群間で有意差を認めた(P=0.003, P=0.029)。また、cancer stem cell 関連因子に関して、CD133、CD24 が共に陽性の症例では low-sensitive 群が多く(87%)、共に陰性の症例では high-sensitive 群が多かった(81%)。その他の感受性マーカーにおいては治療効果との間に関連は認めなかった。

D．考察

cancer stem cell(癌幹細胞)は腫瘍形成能を有する細胞で、自己複製能と分化能を兼ね備える他に抗癌剤や放射線に対する耐性を有しており、癌の転移・再発の根幹に関与しているとされている。本研究では cancer stem cell 関連因子である CD133 と CD24 の発現が局所進行直腸癌に対する術前化学放射線療法の感受性に関与することが明らかとなった。この結果、これら 2 つの感受性マーカーが術前化学

放射線療法の感受性予測因子と成りえる可能性が示された。今後は治療前の腫瘍からの生検標本を用いた prospective study にて cancer stem cell 関連因子が術前化学放射線療法の感受性予測因子と成り得ることを明らかにする必要がある。

E．結論

cancer stem cell 関連因子である CD133 と CD24 の発現が局所進行直腸癌に対する術前化学放射線療法の感受性に関与する。この感受性診断を用いた新しい治療システムの確立が期待される。

F．健康危険情報

なし。

G．研究発表

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2011 2:465-470

H．知的財産権の出願・登録状況

1. 特許取得

特になし。

2. 実用新案登録

特になし。

3. その他

特になし。

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
肛門扁平上皮癌に対する新規化学放射線療法の確立

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研究要旨
稀少疾患である臨床病期 II-III 期肛門管扁平上皮癌に対する根治的化学放射線療法の多施設共同臨床試験において、放射線治療の内容の精度評価・品質管理を行い、臨床試験の質の保証を図っている。本試験は我が国初の肛門管扁平上皮癌に対する根治的化学放射線療法の臨床試験であるため、治療内容のばらつきが懸念されたが、登録 10 例の放射線治療内容の評価では、遵守 80%と治療の質を保つことができている。さらなるプロトコール遵守率の増加のために、施設への逸脱内容のフィードバックと全参加施設への定期的な放射線治療規定の確認の連絡が重要である。

A．研究目的

本研究の目的は、稀少疾患である臨床病期 II-III 期肛門管扁平上皮癌に対する根治的化学放射線療法の多施設共同臨床試験において、放射線治療の内容の精度評価・品質管理を行い、臨床試験の質を保証することである。放射線治療内容の均一化を目指し、経時的にプロトコール遵守率を上げ臨床試験の質を高め、保証することを目標とする。

B．研究方法

研究方法は、「臨床病期 II-III 期肛門管扁平上皮癌に対する S-1+MMC を同時併用する根治的化学放射線療法の臨床第 I/II 相試験：JCOG0903」において、放射線治療の品質保証活動を行うことである。本試験は我が国初の肛門管扁平上皮癌に対する根治的化学放射線療法の臨床試験であるため、プロトコール作成段階において、参加施設予定の放射線治療担当医と臨床試験の内容及び放射線治療規定に関して意思統一を図り、プロトコール本文に明確な放射線治療規定を記載している。試験開始後、登録例において、放射線治療内容の評価に必要な各種診断画像、治療計画情報、位置照準画像、放射線治療照射記録等の資料を登録施設から提出してもらい、放射線治療規定の遵守の程度につき、登録例毎に判定を行う。問題点があれば、登録施設にフィードバックする。

（倫理面への配慮）

本臨床試験は、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則に従って遂行している。説明同意文書を作成し、JCOG プロトコール審査委員会と国立がん研究センター倫理委員会において審査承認された文書で登録前に患者本人に対して十分な説明を行い、文書で同意を得て症例登録を行う。データの取り扱い上、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。JCOG に所属する研究班は共同で、Peer review と外部委員審査を併用した第三者的監視機構としての各種委員会を組織しており、本研究も、JCOG のプロトコール審査委員会、効果・安全性評価委員会、監査委員会、放射線治療委員会などによる第三者的監視を受けることを通じて、倫理性の確保に努めている。

C．研究結果

本試験に登録された第 I 相試験の 10 例について放射線治療内容の確認、評価をした。全例 3 次元放射線治療計画を施行し、放射線治療規定通り 1 回線量 1.8Gy、総線量 59.4Gy で治療されていた。標的体積設定において、全例原発巣と転移リンパ節の囲みは適切であったが、2 例で所属リンパ節領域の囲みに逸脱を認めた。1 例は鼠径リンパ節領域の囲みが小さめであり、他の 1 例は放射線治療規定では設定していない総腸骨リンパ節領域を含めて囲んでいた。また、所属リンパ節領域への予防照射線量において、規定では 36Gy であるが、一部の領域で 45Gy まで照射されている例が 1 例あり、逸脱と判定した。その他、照射方法、線量分布、リスク臓器の線量規定は全例で遵守されていた。総合判定として、8 例（80%）が遵守、2 例（20%）で逸脱であり、違反例はなかった。逸脱例に関しては、逸脱内容について登録施設へフィードバックをした。第 II 相試験開始にあたり、メーリングリストを通じて全参加施設の放射線治療医に、標的体積設定、所属リンパ節領域への予防照射線量などの放射線治療の確認の連絡をした。また、本試験への新規参加施設については、施設の

放射線治療担当医に連絡をとり、放射線治療設備の確認と本試験内容、放射線治療規定の賛同の確認をした。

D．考察

多施設共同で実施する放射線治療を用いるがん臨床試験において、放射線治療内容の較差は臨床試験の結果に影響を及ぼすため、試験内容の質を保証することを目的とした放射線治療の品質保証活動は重要である。本試験でもプロトコール作成段階から品質保証活動を施行している。本年度は登録例に対し、放射線治療内容の評価を施行し、80%の遵守率であることを確認した。逸脱例の2例においても、試験結果に重要な影響を及ぼすものではないが、さらなる放射線治療内容の均一化を図ることが必要である。逸脱の原因は、計画者側で放射線治療規定を十分に理解していなかったことやプロトコール作成段階での放射線治療規定（案）を見て治療計画を施行したことであった。このため、逸脱判明時には登録施設に逸脱内容についてフィードバックをするとともに、全参加施設の放射線治療担当医には、定期的に放射線治療規定の周知の連絡をプロトコール添付とともにすることが必要と考えられた。現在、経時的にプロトコール遵守率が上がるように、品質保証活動を継続している。

E．結論

本試験は稀少疾患である肛門管扁平上皮癌に対して多施設共同で実施している臨床試験であるため、放射線治療の品質保証活動が重要である。現在までに登録例の放射線治療内容の質は保たれている。

F．健康危険情報

なし

G．研究発表

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2. 学会発表

なし

H．知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

特記すべき事項なし

Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
該当なし							

雑誌

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Ⅳ.　研究成果の刊行物・別刷り

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SURGERY TODAY

Original Article

Association Between Incisional Surgical Site Infection and the Type of Skin Closure After Stoma Closure

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Abstract

Purpose. This study was performed to investigate the effect of subcuticular sutures on the incidence of incisional surgical site infection (SSI) after closure of a diverting stoma.

Methods. The study was carried out as a retrospective analysis of prospectively collected data from 51 patients who underwent closure of diverting stoma following resections of lower rectal cancer between January 2008 and December 2008. This study attempted to determine whether there was an association between the type of skin closure and the incidence of incisional SSI. Moreover, risk factors for incisional SSI after closure of diverting stoma were identified using a multivariate analysis.

Results. An incisional SSI occurred in 12 of the 51 patients (23.5%). The rate of incisional SSI with subcuticular sutures was 11.1% (3/27) in comparison to 37.5% (9/24) with transdermal suture and skin stapler. A subcuticular skin closure was the only favorable factor that was significantly associated with a lower incidence of incisional SSI (odds ratio: 0.19; 95% confidence interval: 0.04–0.92).

Conclusions. A subcuticular skin closure has a protective effect against incisional SSI after closure of diverting stoma. A larger study is necessary to further define the role of subcuticular suture on the prevention of incisional SSI in cases of gastrointestinal surgery.

Key words Subcuticular skin closure · Stoma · Surgical site infection

Introduction

Incisional surgical site infection (SSI) is one of the most frequent complications observed after stoma closure,[1] and previous studies have reported that the rate of occurrence of such complications is as high as 40%.[2] Delayed primary closure or healing by secondary intention is recommended to reduce the occurrence rate of this type of infection.[2,3] However, the wounds take several days to be closed with delayed primary closures. Furthermore, they are accompanied by painful dressing changes. Moreover, healing by secondary intention requires a minimum of several weeks for epithelialization.[4] Several recent reports have suggested that subcuticular suturing is associated with a lower incidence of incisional SSI in cardiovascular, orthopedic, and gynecological surgeries.[5–8] Although previous studies have previously reported that subcuticular sutures are preferred from an aesthetic viewpoint,[9] the protective effect of these sutures against incisional SSI has never been reported in gastrointestinal surgery. In particular, the procedures used for stoma closure are potentially at high risk for the occurrence of incisional SSI.

The aims of this study were to describe the association between incisional SSI and the type of skin closure after diverting stoma closure and to examine the protective effect of subcuticular suture against incisional SSI. Moreover, clinicopathological factors were analyzed to identify the risk factors for incisional SSI after closure of diverting stoma using a multivariate analysis.

Patients and Methods

Fifty-one patients underwent closure of diverting stoma at the National Cancer Centre Hospital East (NCCHE), Kashiwa, Japan, between January 2008 and December 2008. Forty-eight of the 51 patients underwent reconstruction during resections for primary rectal cancer, and 3 were emergently constructed after the occurrence of anastomotic leakage. The stomas were usually closed several months following the previous surgery. The surgeon determined whether ileostomy or colostomy had been constructed.

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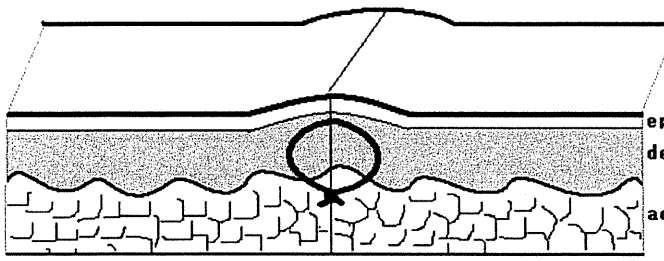

Fig. 1. Schematic illustration of subcuticular sutures. The dermal layer on each edge is properly attached by subcuticular sutures

Stoma Closure Procedures

The skin around the rim of the stoma was excised with 2–3-mm margins, the intestine was mobilized from the abdominal wall, and the stoma was tightly closed with the intestinal mucosa inverted by suturing the skin rim. Intra-abdominal dissections were performed in order to enable complete mobilization of the stomas. The bowels were transected on either side of the stomas, and either stapled functional end-to-end anastomosis or hand-sewn anastomosis was performed.[3] Abdominal fascia was closed with interrupted suturing with a gradually absorbable monofilament material (polydioxanone; Johnson & Johnson, Tokyo, Japan; or Glycomer 631; Covidien, Tokyo, Japan). The wounds were thoroughly irrigated with 300–500 ml of warm saline. Thereafter, the skin was closed by subcuticular suturing with slowly absorbable monofilament material (polydioxanone, or polytrimethylene carbonate; Covidien) as illustrated in Fig. 1, interrupted transdermal suturing using 4-0 nylon, or a skin stapler (Visistat; Teleflex Medical, Durham, NC, USA). No drains were placed in the abdominal cavity.

Perioperative Care

Patients received mechanical bowel lavage treatment with 180 ml of magnesium citrate (Magcorol P; Horii-Yakuhin, Osaka, Japan) for 2 days before the surgery. No chemical bowel preparation was applied. Patients were administered two doses of cefmetazole sodium (CMZ) — a second-generation cephalosporin — as a prophylactic antibiotic. One gram of CMZ was administered to patients within 30 min prior to the skin incision; thereafter, the same dose of the drug was administered 3 h later. Clear liquid intake was allowed in patients on postoperative day (POD) 2, soft food intake was allowed on POD 4, and the patients were discharged from the hospital after removal of nonabsorbable sutures or staples on POD 7 or 8.

SSI Surveillance

Incisional SSI was defined, according to the guidelines issued by the Centers for Disease Control and Prevention, as any infection that involved the skin and subcutaneous soft tissue around incisions within 30 days after the operation,[10] and it included at least one of the following: (1) an infection accompanied by apparently purulent discharge with or without laboratory evidence; (2) culture-positive drainage fluid or soft tissue from the incision; (3) the incision had signs of inflammation, was deliberately opened by a surgeon, and the culture was positive. The wounds were inspected for any problem twice a day during admission and at the outpatient clinic at least once, 30 days after surgery. Incisional SSI was identified retrospectively by an infection-control team that thoroughly reviewed clinical records of patients who underwent stoma closure. All data regarding SSI were prospectively recorded in a database and were analyzed as a retrospective cohort study.

Statistical Analysis

The data were collected in a database for analysis (SPSS 11.0 J for Windows; SPSS, Chicago, IL, USA). Differences between numerical variables were tested using the Mann–Whitney *U*-test and those between categorical variables were tested using chi-square statistics. The multivariate analysis was performed using a logistic regression model. A P value of less than 0.05 was considered to be significant.

Results

Fifty-one patients underwent stoma closure at NCCHE, Kashiwa, Japan during the period of study. The procedures followed for the primary operation included abdominoanal resection ($n = 29$), low anterior resection ($n = 20$), total colectomy ($n = 1$), and pelvic exenteration ($n = 1$). Twelve of the 51 patients (23.5%) developed incisional SSI. Bacteria identified from the incisions with positive SSIs included methicillin-resistant *Staphylococcus aureus* ($n = 2$), *Escherichia coli* ($n = 1$), *Enterococcus faecium* ($n = 1$), *Enterococcus faecalis* ($n = 1$), *Enterococcus raffinosus* ($n = 1$), and *Enterococcus avium* ($n = 1$). The median postoperative day on which patients

Table 1. Clinical background of patients according to the type of skin closure

Factor		Subcuticular ($n = 27$)	Staple and transdermal ($n = 24$)	P value
Age (years)	Mean ± SEM	60.2 ± 2.5	63.5 ± 2.1	0.30
Sex (n)	Male/Female	23/4	15/9	0.06
ASA score (n)	1/2	14/12	12/12	0.50
Total protein (g/dl)	Mean ± SEM	6.9 ± 0.1	6.9 ± 0.1	0.62
Albumin (g/dl)	Mean ± SEM	4.1 ± 0.0	4.0 ± 0.1	0.97
DM	+/–	3/24	4/20	0.43
BMI (kg/m^2)	Mean ± SEM	22.4 ± 0.5	22.0 ± 0.7	0.52
Type of stoma (n)	Colostomy/Ileostomy	3/24	12/12	<0.01
Type of anastomosis (n)	FEEA/hand-sewn	26/1	24/0	0.53
Blood loss (g)	Mean ± SEM	56.8 ± 10.5	60.0 ± 7.8	0.29
Operation time (min)	Mean ± SEM	81.2 ± 6.8	72.7 ± 9.7	0.68
Body temperature[a] (°C)	Mean ± SEM	36.4 ± 0.1	36.3 ± 0.1	0.63

There were no statistical differences in the background except for the type of stoma
SEM, standard error of the mean, ASA, American Society of Anesthesiology, DM, diabetes mellitus; BMI, body mass index; FEEA, functional end-to-end anastomosis
[a] Body temperature is demonstrated as the lowest value recorded during operation

Table 2. Analysis of variables associated with incisional surgical site infection (SSI)

Factor		SSI(+) ($n = 12$)	SSI(–) ($n = 39$)	P value
Age (years)	Mean ± SEM	65.7 ± 2.9	60.5 ± 1.9	0.20
Age ≥70 (n)	+/–	6/6	10/29	0.11
Sex (n)	Male/Female	10/2	28/11	0.35
ASA score (n)	1/2	6/6	21/18	0.57
Total protein (g/dl)	Mean ± SEM	6.9 ± 0.1	6.9 ± 0.1	0.51
Albumin (g/dl)	Mean ± SEM	4.1 ± 0.1	4.1 ± 0.0	0.51
DM	+/–	2/10	5/34	0.53
BMI (kg/m^2)	Mean ± SEM	21.7 ± 0.8	22.3 ± 0.5	0.63
Type of stoma (n)	Colostomy/Ileostomy	5/7	10/29	0.24
Type of anastomosis (n)	FEEA/hand-sewn	11/1	39/0	0.24
Type of skin closure	Subcuticular/Staple or transdermal	3/9	24/15	0.03
Blood loss (g)	Mean ± SEM	69.8 ± 16.3	54.7 ± 7.0	0.56
Operation time (min)	Mean ± SEM	85.2 ± 14.6	74.7 ± 6.1	0.59
Body temperature[a] (°C)	Mean ± SEM	36.2 ± 0.2	36.4 ± 0.1	0.51

A lower rate of incisional SSI was observed with subcuticular skin closure than with stapler or transdermal closure. All other factors were insignificant
[a] Body temperature is demonstrated as the lowest value recorded during operation.

were diagnosed with incisional SSI was day 5. Eleven patients were diagnosed with incisional SSI during admission and the remaining patient was diagnosed after discharge. All incisional SSIs were treated by wound opening, drainage, and irrigation with normal saline.

Table 1 presents the clinical background of patients on the basis of the type of skin closure. The subcuticular suture group underwent a greater number of ileostomy procedures than the stapler/transdermal suture group. No statistical differences of background between the two groups were found in other clinical factors. Table 2 presents the associations between clinical factors and incidence of incisional SSI. A lower rate of incisional SSI was observed with subcuticular skin closure than with stapler or transdermal closure ($P = 0.03$). There was a trend toward a higher rate of incisional SSI in patients older than 70 years ($P = 0.11$).

The multivariate analysis showed that the type of skin closure was the only independent factor associated with incidence of incisional SSI (Table 3). The rate of the incisional SSI decreased from 37.5% in cases closed by transdermal sutures or staples to 11.1% in those closed with subcuticular sutures (odds ratio: 0.19; 95% confidence interval: 0.04–0.92). No statistically significant difference was observed in the postoperative length of the hospital stay between patients with or without subcuticular sutures (the median postoperative hospital stay in both groups was 8 days; $P = 0.96$). A postoperative reoperation was required in 3 (5.9%) of 51 patients due

Table 3. Multivariate analysis of the risk factors of incisional SSI after closure of diverting stoma

Factor		Odds ratio	(95% CI)	*P* value
Type of stoma	Ileostomy	1		
	Colostomy	1.26	(0.26–6.1)	0.78
Age	<70	1		
	≥70	3.25	(0.73–14.4)	0.12
Type of skin closure	Staple or transdermal suture	1		
	Subcuticular suture	0.19	(0.04–0.92)	0.04

The multivariate analysis demonstrated that the type of skin closure was the only independent factor associated with incidence of incisional SSI
CI, confidence interval

to associated complications, i.e., anastomotic leakage in one case, and intestinal obstruction in the other two patients. No mortalities were observed in this series.

Discussion

Several randomized controlled trials have indicated the protective effects of subcuticular skin closure against incisional SSI in cases of clean surgery.[5,6] Furthermore, some retrospective studies showed that subcuticular suturing is associated with a significantly lower rate of incisional SSI in clean-contaminated wounds following gynecological surgery.[7,8] However, there is no available evidence to support the protective effects of subcuticular suturing against incisional SSI in gastrointestinal surgery, in which the incidence of incisional SSI is rather high. This study is the first to clearly demonstrate that subcuticular suturing reduces the rate of incisional SSI in gastrointestinal surgery.

Although several reports noted the protective impact of subcuticular suturing against incisional SSI,[5–8] none of them clearly explained the mechanism underlying the effect. Subcuticular skin closure approximates the skin by tightly connecting both edges at the level of the dermis; thereafter, suture strings are buried beneath the surface of the skin. This prevents subcutaneous dead space and excessive tissue inflammation, both of which are risk factors of incisional SSI.[11] On the contrary, improper placement of skin staples disturbs the normal contact between the dermis and adipose tissues, which causes subcutaneous dead space and prevents proper wound healing.[12,13] Transdermal suturing with nonabsorbable material might also prevent the formation of subcutaneous dead space, but it is likely to cause excessive inflammation because it penetrates the dermal barrier with foreign material. Transdermal suturing is also likely to damage fragile adipose tissue, because it holds the dermis and subcutaneous tissue together with the same tensile strength.[14] Therefore, subcuticular suturing is superior to skin staples and transdermal suturing because it helps the wound-healing process. Subcuticular skin closure also supports the reconstruction of the dermis. Capillary vessel loops in the dermis provide the main blood supply to cutaneous wound healing while collagen formation in the dermis offers tensile strength to the wound.[15–17] Therefore, proper reconstruction of the dermis is the critical process in the restoration of cutaneous function. The appropriate contact of dermis achieved by subcuticular suturing may promote proper wound healing and restoration of cutaneous function, which, in turn, enhances host defense against infection.[11]

A univariate analysis showed that subcuticular suturing was the only factor that was associated with the incidence of incisional SSI. Although the elderly had an increased likelihood of developing incisional SSI, as seen in previous studies,[18,19] the results did not show statistical significance. In addition, contrary to previous reports,[20] colostomy closure was not associated with a higher incidence of incisional SSI. A multivariate analysis was performed to exclude the possible confounding effect among these three factors. The results clearly demonstrated that subcuticular suturing had the greatest effect in preventing incisional SSI among clinical factors previously reported to be associated with incisional SSI.

The current study has several limitations. First, SSI was identified retrospectively by daily chart review of the infection control doctor. Detection by chart review is suggested to be a less accurate method than direct observation of surgical sites.[10] However, chart review is the most widely employed method of SSI surveillance in the medical literature.[2,7,18,19,21] The reported sensitivity of this method is as high as 83.8%–92.3% in comparison to prospective direct SSI surveillance.[22] Therefore, the surveillance method did not preclude the importance of the findings in the current series. Second, this study was a single-center study, and it involved a relatively small number of cases. Although a multivariate analysis revealed an association between subcuticular suturing and the incidence of incisional SSI, a larger, more scientific study is warranted. A multicenter, randomized controlled trial is currently under way to confirm the effect

of subcuticular suturing on the incidence of incisional SSI in gastrointestinal surgery.

In conclusion, subcuticular suturing was found to have a protective effect against incisional SSI after diverting stoma closure. This study was the first to report the effect of subcuticular suturing on the prevention of incisional SSI in gastrointestinal surgery. A large multicenter randomized controlled trial is ongoing to confirm the role of subcuticular suturing in preventing incisional SSI in gastrointestinal surgery.

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A Phase I/II Trial of Chemoradiotherapy Concurrent with S-1 plus Mitomycin C in Patients with Clinical Stage II/III Squamous Cell Carcinoma of Anal Canal (JCOG0903: SMART-AC)

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A Phase I/II trial of chemoradiotherapy concurrent with S-1 plus mitomycin C in patients with clinical Stage II/III squamous cell carcinoma of the anal canal was started in Japan. The aim of this trial is to determine the recommended dose of S-1 combined with a fixed dose of mitomycin C plus radiotherapy in Phase I and to evaluate the efficacy and safety in Phase II. The primary endpoint for the Phase II part of this study is the proportion of 3-year event-free survival, in which the following are defined as events: disease progression, residual tumor at the end of chemoradiotherapy, colostomy or death, whichever comes first. Secondary endpoints are progression-free survival, proportion of complete response and adverse events. In the Phase II part of this study, a total of 65 patients will be enrolled from 42 institutions over 6 years.

Key words: anal canal cancer – chemoradiotherapy – S-1 – mitomycin C – radiotherapy

INTRODUCTION

Anal canal cancer is extremely rare in Japan: only 313 patients died of it in 2007 (1). In the USA, it is also a relatively rare disease: there were 5290 patients (~2 per 100 000) in 2009 (2). However, the incidence in the USA has doubled over the last 30 years and is expected to increase in the future. Considering the current situation in the USA, the incidence of anal cancer might rise in Japan.

For Stage II/III squamous cell carcinoma of the anal canal, there have been no clinical trials comparing surgery and concurrent chemoradiotherapy (CRT); however, CRT has been recognized as the standard treatment globally. This is because squamous cell carcinoma of the anal canal is sensitive to CRT and CRT can preserve the anal function, and residual or recurrent tumor can be safely resected by salvage surgery. The combination of 5-fluorouracil (5-FU) plus mitomycin C (MMC) concurrent with radiotherapy has shown better outcomes than radiotherapy alone or 5-FU with radiotherapy. Recently, two Phase III trials failed to show the superiority of 5-FU plus cisplatin over 5-FU plus MMC (3,4). On the basis of these results, 5-FU plus MMC is considered as the current standard regimen of CRT.

S-1 is an oral fluoropyrimidine, for which non-inferiority to 5-FU was reported in gastric cancer (5). In addition, it was reported that S-1 enhanced the effect of radiotherapy *in vivo* model (6). Oral drugs are clearly more convenient than parenteral preparations. If the combination of S-1 plus MMC has similar efficacy to 5-FU plus MMC, we can regard S-1 plus MMC as the new standard treatment.

The first aim of this study is to determine the recommended dose (RD) of S-1 in Phase I because we have no experience of CRT concurrent with S-1 plus MMC. The second aim of this study is to evaluate the efficacy and safety in Phase II. After the present study, we have not planned a Phase III study comparing 5-FU and S-1 because there are only a few anal cancer patients in Japan. In the

survey of the Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG), there were only 59 eligible patients over the last 5 years (7). When the proportion of 3-year event-free survival (EFS), which is the primary endpoint of this study, is proven to be satisfactory, we can regard this combined treatment as the new standard treatment for Stage II/III squamous cell carcinoma of the anal canal, which means that this study is a non-randomized confirmatory study.

The Protocol Review Committee of the JCOG approved this study protocol in January 2010 and the study was initiated in February 2010. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000003237 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGESTS OF JCOG 0903

Objectives

Phase I part

To evaluate the maximum tolerated dose and dose-limiting toxicities (DLTs) to determine the RD of S-1 in combination with a fixed dose of MMC plus radiation therapy in patients with Stage II/III squamous cell carcinoma of the anal canal.

Phase II part

To evaluate the efficacy and safety of combination CRT with S-1 plus MMC in patients with Stage II/III squamous cell carcinoma of the anal canal.

Study Setting

A multi-institutional open-label Phase I/II trial.

Resources

This study is supported by Grants-in-Aid for Cancer Research (20S-3, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

Phase I part

The primary endpoint is the number of patients with DLT. The secondary endpoint is the incidence of adverse events.

Phase II part

The primary endpoint is the proportion of 3-year EFS in all eligible patients, including the patients who received the level of RD in the Phase I part. EFS is defined from the date of registration to the date of death from any cause, first evidence of disease progression, evaluated as non-complete response (CR) at the second evaluation after CRT, undergoing colostomy or first evidence of second primary cancer, whichever comes first. It is censored at the last follow-up day when the patient is alive without any events. The definition of EFS is identical to that in RTOG9811.

The secondary endpoints are the proportion of CR, progression-free survival, EFS, overall survival, colostomy-free survival and incidence of adverse events. Progression-free survival is defined from the date of registration to the date of disease progression or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of progression. Colostomy-free survival is defined from the date of registration to the date of undergoing colostomy or death from any cause.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, patients are required to fulfill all of the following criteria:

(i) Lesion located in the anal canal by endoscopic evaluation
(ii) Histologically proven squamous cell carcinoma or basaloid carcinoma
(iii) Clinical Stage II/III (TNM-UICC 6th, 2002)
(iv) Phase I part: aged 20–75 years old, Phase II part: aged 20–80 years old
(v) ECOG performance status of 0 or 1
(vi) Having measurable lesion is not mandatory
(vii) No previous therapy against anal canal cancer except simple colostomy 7 days or more before registration
(viii) Neither previous chemotherapy, CRT nor radiotherapy against any cancer
(ix) Sufficient oral intake
(x) Adequate organ functions
(xi) Written informed consent

Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

(i) Simultaneous or metachronous (within 5 years) double cancers, with the exception of intramucosal tumor curable with local therapy
(ii) Patients requiring the administration of phenytoin or warfarin potassium
(iii) Pregnant or lactating women or women of childbearing potential
(iv) Psychosis
(v) Requiring systemic steroid medication
(vi) Serum HBs antigen-positive
(vii) Anti-HIV antibody-positive

(viii) Uncontrollable diabetes mellitus or continuous use of insulin
(ix) Uncontrollable hypertension
(x) Unstable angina, heart failure or with a history of myocardial infarction within 6 months
(xi) Interstitial pneumonitis, lung fibrosis or severe emphysema
(xii) Active bacterial or fungal infection
(xiii) Body temperature over 38°C

Registration

After confirmation of fulfillment of the eligibility criteria, registration is made by telephone or fax to the JCOG Data Center.

Treatment Methods

Chemotherapy

Combined CRT consists of S-1, MMC and radiotherapy. S-1 is orally administered twice per day from days 1 to 14 and days 29 to 42. There are three dose levels of S-1 in the Phase I part of this study: 40, 60 and 80 mg/m^2/day. The RD of S-1 is determined in the Phase I part and the RD is administered in the Phase II part of this study. MMC is infused on days 1 and 29 with a fixed dose, 10 mg/m^2/day.

Radiotherapy

Radiotherapy is delivered with megavoltage (≥6 MV) X-rays using a multiple-field technique. Patients receive 1.8 Gy/day of radiation for 5 days per week from the initiation of chemotherapy, and the total radiation dose is 59.4 Gy. Three-dimensional computed tomography (CT) simulation is required. The clinical target volume (CTV) includes the primary tumor plus 1–2 cm craniocaudally and 0.5–1 cm circumferentially, the metastatic lymph node and regional lymph nodes. The regional lymph nodes include the mesorectum with pararectal lymph nodes, sacral, internal iliac, obturator, external iliac and inguinal lymph nodes. Planning target volume (PTV) is defined as CTV plus 0.5–1 cm margins for uncertainty. After PTV has been treated up to a dose of 36.0 Gy, an additional dose of 23.4 Gy is given to a reduced irradiation volume, including only primary tumor and metastatic lymph nodes with margins, for a total dose of 59.4 Gy.

Dose Escalation Method

In the Phase I part of this study, there are three dose levels of S-1 as follows: Level −1 at 40 mg/ m^2/day, Level 0 at 60 mg/m^2/day and Level 1 at 80 mg/m^2/day. Level 0 is the starting dose, and initially three patients are administered. The schema of dose escalation is shown in Fig 1.

Definition of DLT

DLT is defined by the following criteria. The observation period of DLT is between the date of initiating CRT and the date of 14 days after the last radiotherapy. Severity of toxicity is assessed according to the Common Terminology Criteria for Adverse Events v 3.0 (CTCAE v3.0).

(i) Grade 4 neutrophils lasting ≥8 days
(ii) Grade 4 platelets
(iii) Grade 3 febrile neutropenia lasting ≥4 days
(iv) Grade 3 infection with Grade 3 or 4 absolute neutrophil count (ANC) lasting ≥4 days
(v) Grade 3 infection with normal ANC lasting ≥4 days
(vi) Grade 3 diarrhea lasting ≥3 days despite supportive care
(vii) Grade 4 non-hematologic toxicity except for dermatitis chemoradiation, alkaline phosphatase, γ-glutamyltranspeptidase, hyperglycemia, hypercalcemia, hypocalcemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypomagnesemia, hypophosphatemia, cholesterol and hypertriglyceridemia,
(viii) Unable to receive S-1 ≥15 times per course
(ix) Delay of starting the second course for ≥8 days
(x) Unable to complete the protocol treatment within 66 days from the initiation of CRT

Efficacy Evaluation and Follow-up

All patients are assessed at 8 and 12 weeks after the end of CRT by abdominal and pelvic CT, pelvic magnetic resonance imaging (MRI) and colonoscopy. We classify as CR of overall response if both of the following criteria are met: no cancer cells are detected by biopsy from the primary site and no tumors are detected by CT, MRI and colonoscopy. Overall responses at both 8 and 12 weeks after the end of CRT are evaluated as CR; we define the best overall response as CR. When overall response is evaluated as first CR at 12 weeks after the end of CRT, the additional evaluation for confirmation will be performed at 16 weeks after the end of CRT.

Salvage surgery is recommended when disease progression is observed before the evaluation, the best response is non-CR at 12 or 16 weeks after the end of CRT or local recurrence is found after CRT.

Adverse events are evaluated at least every week during protocol treatment using CTCAE v3.0. After protocol treatment, patients are followed up every 4 months for 3 years and every 6 months for 5 years.

Study Design and Statistical Analysis

This study is a Phase I/II trial to determine the RD of S-1 in combination with a fixed dose of MMC plus radiotherapy in the Phase I part and to evaluate the efficacy and safety in the Phase II part.

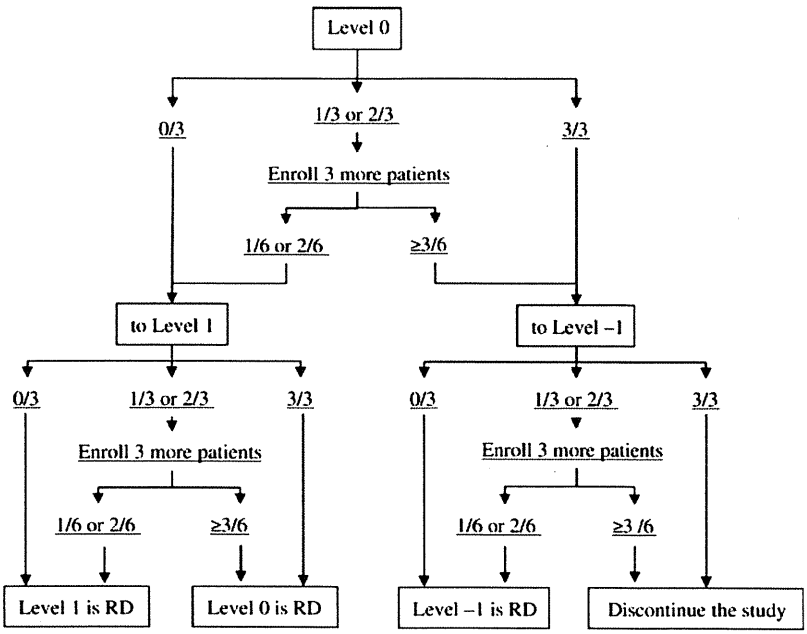

Figure 1. Schema of dose escalation. #/#, the number of patients with dose-limiting toxicity/total number of patients; RD, recommended dose.

The sample size in the Phase II part of this study is 65, including the RD level in the Phase I part. This sample size provides 80% power under the hypothesis of the expected value of the primary endpoint of 75% and the threshold value of 60% using one-sided testing at a 5% one-sided significance level. To test the hypothesis, % 3-year EFS estimated by the Kaplan–Meier method and its confidence interval (CI) by Greenwood's formula are used.

S-1 is expected to be more toxic than 5-FU, but we expect that the frequency of neutropenic fever, which is the clinically meaningful toxicity, will be almost equivalent (<20%). On the other hand, the convenience for the patients will be increased by using S-1. Therefore, we consider CRT concurrent with S-1 plus MMC as an equivalently toxic and more convenient regimen. When the lower limit of 90% CI with % 3-year EFS is above 60% and the safety profiles are as low as expected, we can conclude that the CRT concurrent with S-1 plus MMC is the new standard treatment for anal cancer.

Interim Analysis and Monitoring

In the Phase II part of this study, we planned an interim analysis once during the trial when 25 patients are registered. The aim of interim analysis is to evaluate the futility. When the upper limit of 90% CI with % 1-year EFS is below 75%, this study will be discontinued.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate the study progress and to improve the study quality.

PARTICIPATING INSTITUTIONS

The participating institutions (from north to south) are as follows: Sapporo-Kosei General Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital,* Ibaraki Prefectural Central Hospital and Cancer Center, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center,* National Cancer Center Hospital East,* Chiba Cancer Center Hospital, Jyuntendo Urayasu Hospital, National Cancer Center Hospital,* Kyorin University School of Medicine,* Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital,* Keio University Hospital,* Tokyo Medical and Dental University Hospital, Kitasato University East Hospital,* Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kitasato University School of Medicine, Showa University Northern Yokohama Hospital, Niigata Cancer Center Hospital, Ishikawa Prefectual Central Hospital, Nagano Municipal Hospital, Shizuoka Cancer Center,* Aichi Cancer Center Hospital,* Fujita Health University, National Hospital Organization Kyoto Medical Center,* Osaka University Graduate School of Medicine,* Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases,* Osaka National Hospital, Osaka Medical College, Sakai Municipal Hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Hyogo College of Medicine, Hiroshima University Hospital,* Hiroshima City Hospital, National Hospital Organization Shikoku Cancer Center,* Kurume University School of Medicine* and Oita University Faculty of Medicine.*

*Institutions that participated from the Phase I part.

Conflict of interest statement

None declared.

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症例報告 I

成人の前仙骨部に発生した類皮嚢腫（epidermoid cyst）の2例

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症例は婦人科癌検診で骨盤腔内腫瘤を指摘され，当院受診した27歳と28歳の女性である．MRI検査では，それぞれ直腸左側に5 cm大と6 cm大の病変を認め，T2強調像で境界明瞭な高信号を呈する嚢胞性腫瘤を認めた．CT検査では，辺縁に被膜様濃染を認め，明らかな実質構造は認めなかった．2例とも前仙骨部嚢胞性腫瘍と診断し，尾骨合併切除による経仙骨的アプローチにより完全切除を施行した．病理組織学的検査で嚢胞壁内面に重層扁平上皮を認めたが，皮膚付属器構造を認めず類皮嚢腫と診断した．術後は，排便機能障害や再発を認めずに経過している．

前仙骨部は胎児性組織の遺残物より種々の腫瘤が出現する．胎生期の発達異常に伴うものはdevelopmental cystと言われ，dermoid cyst，epidermoid cyst，tail gut cystに分類される．これらは希ではあるが悪性化の報告もあり，腫瘤の外科的完全切除が望ましい．しかし，本邦での術式の選択基準は確立されておらず，今後更なる検討が必要である．

索引用語：presacral space，epidermoid cyst，developmental cyst

はじめに

仙骨前面と直腸後面に囲まれた前仙骨部（以後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いる．そのため，様々な腫瘤が発生する可能性の高い場所とされている．前仙骨部に発生する腫瘤は小児期に指摘されることが多く，成人発症例は比較的まれである．今回，成人の前仙前部に発生した類表皮嚢腫の2例を経験したので，本邦での報告例を集計し文献的考察を加えて報告する．

症　例

症例1：27歳，女性．

主訴：なし．

既往歴：特記すべきことなし．

現病歴：婦人科癌検診で内診を受け，腫瘤を触知された．骨盤内腫瘍の疑いで精査・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112/60mmHg，脈拍56/分，整．体温36.7℃．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 1.3ng/m*l*，CA19-9 16U/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5 cm大の腫瘤性病変を認めた．造影CT検査では腫瘤内部や壁に増強効果を認めず，隔壁構造や壁肥厚も認めなかった（Fig. 1a）．

骨盤MRI検査：CT検査と同様に，下部直腸の左側にT1強調像でやや高信号，T2強調像で高信号を示す内部が均一な腫瘤性病変を認めた．ガドリニウム造影では内部に明らかな造影効果を認めなかった（Fig. 1b）．

大腸注腸造影検査および大腸内視鏡検査：下部直腸の左側に軽度の圧排像を認めたが，粘膜面には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