様式第１９

学 会 等 発 表 実 績

委託業務題目：「大腸がん肝転移切除例に適した新規抗がん剤を用いた術後補助化学療法の研究」

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
直腸癌局所再発巣の病理組織学的所見は予後予測因子になりえるか？ワークショップ（口頭）	小森 康司、木村 賢哉、木下 敬史、佐野 力、伊藤 誠二、安部 哲也、千田 嘉毅、三澤 一成、伊藤 友一、植村 則久、川合 亮佑、大澤 高陽、舎人 誠、川上 次郎、浅野 智成、岩田 至紀、倉橋 真太郎、清水 泰博	第114回日本外科学会定期学術集会	2014. 4	国内
肝転移単独を除くStage IV大腸癌の当科における治療成績（口頭）	木村 賢哉、木下 敬史、小森 康司、川合 亮介、植村 則久、伊藤 友一、三澤 一成、千田 嘉毅、安部 哲也、伊藤 誠二、佐野 力、清水 泰博	第114回日本外科学会定期学術集会	2014. 4	国内
S状結腸癌術後に肝・膵・肺転移を切除した１例（口頭）	岩田 至紀、清水 泰博、佐野 力、千田嘉毅、伊藤 誠二、小森 康司、安部 哲也、三澤 一成、伊藤 友一、木村 賢哉、木下 敬史、植村 則久、川合 亮、大澤 高陽、川上 次郎、浅野 智成、倉橋 真太郎、篠田 雅幸、木下 平	第287回東海外科学会	2014. 5	国内
術前化学療法の適応別にみた大腸癌肝転移の検討（口頭）	浅野 智成 清水 泰博、佐野 力、千田 嘉毅、伊藤 誠二、小森 康司、安部 哲也、三澤 一成、伊藤 友一、木村 賢哉	第69回日本消化器外科学会総会	2014. 7	国内
大腸癌肝転移に対する化学療法後肝切除の現状シンポジウム（口頭）	千田 嘉毅 清水 泰博、佐野 力、伊藤 誠二、小森 康司、安部 哲也、三澤 一成、伊藤 友一、木村 賢哉、木下 敬史、植村則久、川合亮佑、木下 平	第52回日本癌治療学会学術集会	2014. 8	国内
大腸癌肝転移における化療後肝切除の安全性～化学療法および休薬によるＩＣＧの変化（ポスター）	千田嘉毅、清水泰博、佐野力、伊藤誠二、小森康司、安倍哲也、三澤一成、伊藤友一、木村賢哉、木下敬史、植村則久、川合亮佑、木下 平	第12回日本消化器外科学会大会	2014. 10	国内
大腸癌肝転移に対する再肝切除例の治療成績ワークショップ（口頭）	岩田至紀、千田嘉毅、夏目誠治、伊藤誠二、小森康司、安倍哲也、三澤一成、伊藤友一、木村賢哉、木下敬史、植村則久、川合亮佑、清水泰博	第76回 日本臨床外科学会総会	2014. 11	国内
術前化学療法の適応別にみた大腸癌肝転移の検討（口頭）	浅野智成、清水 泰博、佐野 力、千田 嘉毅、伊藤 誠二、小森 康司、安部 哲也、三澤 一成、伊藤 友一、木村 賢哉	第69回日本消化器外科学会総会	2014. 7	国内
大腸癌肝転移における門脈塞栓術後の肝肥大についての検討（ポスター）	中山 雄介，後藤田 直人，加藤 祐一郎，高橋 進一郎，小西 大	和歌山・第26回日本肝胆膵外科学会学術集会	2014. 6	国内
脾彎局部結腸癌に対する腹腔鏡下手術における戦略	滝口 伸浩，早田 浩明，外岡 亨，傳田 忠道	京都 第114回日本外科学会雑	2014. 3	国内
大腸癌研究会プロジェクト研究:低位前方切除術における一時的人工肛門造設に関する多施設前向き研究より	齋藤 典男 塩見 明生、小森 康司、坂口 善久、坂本 一博、斉田 芳久、池 秀之、滝口 伸浩、益子 博幸、伊藤 雅昭	郡山 第69回日本消化器外科学会総会	2014. 7	国内
局所進行直腸癌に対する集学的治療 術前化学療法と術前照射療法の治療選択と効果の相違	滝口 伸浩，早田 浩明，外岡 亨，傳田 忠道	横浜 第69回日本大腸肛門病学会学術集会	2014. 9	国内
潰瘍性大腸炎に対する結腸全摘回腸直腸吻合術後の残存直腸に発生した側方リンパ節転移を伴う直腸癌の1例	外岡 亨，滝口 伸浩，早田 浩明，傳田 忠道	横浜 第69回日本大腸肛門病学会学術集会	2014. 9	国内
下部直腸癌における外科治療のダイナミズ	金光幸秀、志田大、塚本俊輔	第114回日本外科学会	2014. 4	国内

術前3DシミュレーションとCT colonograp	金光幸秀、塚本俊輔、坂本	第69回日本消化器外科学会総会	2014. 7	国内
郭清効果からみた下部直腸癌に対する側方	金光幸秀, 志田大, 塚本俊輔,	第76回日本臨床外科学会総会	2014. 11	国内
Correlation between DNA copy number and clinicopathological features: Biomarker search using genome-wide analysis of DNA copy number alterations in a phase Ⅲ study of postoperative adjuvant chemotherapy for stage Ⅲ colon cancer (ACTS-CC trial). (ポスター)	Ishikawa T, Uetake H, Murotani K, Kobunai T, Ishiguro M, Matsui S, Sugihara K.	ヨーロッパ臨床腫瘍学会	2014. 11	国外
高齢者におけるS-1、UFT+LVを用いた結腸癌術後補助化学療法の有効性：aCTS-CC trial年齢別解析. (口演)	石黒めぐみ、中谷英仁、石川敏昭、植竹宏之、杉原健一.	第81回大腸癌研究会	201472	国内
大腸癌化学療法の新展開. (口演)	植竹宏之	消化器外科学会	2014. 10	国内
大腸癌におけるMembrane-type 1 matrix metaloprotease遺伝子としての有用性の検討	金澤周、大島貴、塩澤学、佐藤勉、山本直人、利野靖、国崎主税、吉川貴己、赤池信、今田敏夫、益田宗孝	第100回日本消化器病学会	2014. 4	国内
StageⅢb大腸癌手術例の再発部位・再発危険因子に関する検討	沼田幸司、塩澤学、浅利昌大、片山雄介、澤崎翔、五代天偉、樋口晃生、森永聡一郎、利野靖、益田宗孝、赤池信	第22回日本消化器関連学会週間JDDW2014	2014. 10	国内
進行再発大腸癌1stline化学療法における抗VEGF抗体と抗EGFR抗体の腫瘍縮小率に関する検討	村田一平、塩澤学、浅利昌大、片山雄介、沼田幸司、澤崎翔、樋口晃生、五代天偉、森永聡一郎、赤池信	第114回日本外科学会定期学術集会	2014. 4	国内
原発巣切除後に肝機能増悪を認めた大腸癌肝転移症例に対しL-OHPベースの抗がん剤治療を行い軽快した3例	澤崎翔、塩澤学、樋口晃生、浅利昌大、片山雄介、沼田幸司、五代天偉、利野靖、益田宗孝、赤池信	第52回日本癌治療学会学術集会	2014. 8	国内
大腸癌肝転移症例に対するOptimal morphologic responseを用いた化学療法効果判定の有用性	樋口晃生、塩澤学、浅利昌大、村川正明、片山雄介、澤崎翔、青山徹、金澤周、利野靖、益田宗孝、赤池信	第69回日本大腸肛門病学会総会	2014. 11	国内
コロンモデルを用いた大腸内視鏡挿入法（口頭）	工藤進英	日本消化器病学会総会　東京国際フォーラムGブロック6F「G602」	2014. 4	国内
Detection of Depressed and Flat Lesions	工藤進英	DDW WEOシカゴHilton Hotel	2014. 5	国外
早期大腸癌の拡大内視鏡診断と近未来（口頭）	工藤進英	日本消化器内視鏡学会関東地方会シェーンバッハサボー1F　第1会場	2014. 6	国内
直腸癌に対する側方リンパ節郭清施行例における無再発生存期間の検討、ポスターセッション(196)	山川雄士, 山口智弘, 佐藤純人, 賀川弘康, 富岡寛行, 塩見明生, 金本秀行, 坂東悦郎, 寺島雅典, 上坂克彦, 絹笠祐介	第114回日本外科学会定期学術集会、京都	2014. 4	国内
大腸癌同時性多臓器転移症例に対し治癒切除を目的とした原発巣切除症例の治療成績、ポスターセッション(195)	富岡寛行, 絹笠祐介, 塩見明生, 山口智弘, 賀川弘康, 山川雄士, 佐藤純人, 伊江将史, 前田哲生, 佐藤力弥, 岡ゆりか, 古谷晃伸, 仲井希, 坂東悦郎, 金本秀行, 寺島雅典, 上坂克彦	第114回日本外科学会定期学術集会、京都	2014. 4	国内
Short/Long-Term Outcomes of Conversion Therapy for Unresectable Liver Metastasis of Colorectal Cancer、ポスター	Kagawa H, Kinugasa Y. Shiomi A, Yamaguchi T, Tomioka H	11thInternational Conference of the Asian C	2014.5	国外

切除不能進行癌・再発癌による消化管閉塞に対する緩和手術の検討、要望演題62	富岡寛行，賀川弘康，山口智弘，塩見明生，坂東悦郎，金本秀行，寺島雅典，上坂克彦，絹笠祐介	第69回日本消化器外科学会総会、郡山市	2014.7	国内
StageⅢ大腸癌における5-FU関連酵素等の発現量と臨床病理学的因子の関連：B-CAST、口演92	石黒めぐみ，的場周一郎，絹笠祐介，田中千弘，神藤英二，石田文生，池秀之，裕彰一，畑泰司，望月泉，小澤平太，堀江久永，山口明夫，中谷英仁，杉原健一	第52回日本癌治療学会学術集会、横浜市	2014.8	国内
当院での直腸癌に対する左結腸動脈非温存・温存腹腔鏡下D3リンパ節郭清の比較検討、一般演題282	仲井希，塩見明生，佐藤純人，山川雄士，賀川弘康，富岡寛行，山口智弘，寺島雅典，上坂克彦，絹笠祐介	第27回日本内視鏡外科学会総会、盛岡市	2014.10	国内
Quality control by photograph for evaluation of open (OP) and laparoscopic (LAP) colectomy with D3 resection for stageⅡ/Ⅲ colorectal cancer:Japan Clinical Oncology Group study JCOG 0404. (ポスター)	K Nakajima, M Inomata, T Akagi, T Etoh, H Katayama, M Ito, S Fujii, S Saito, F Konishi, Y Saida, H Hasegawa, T Yamaguchi, Y Fukunaga, K Sugihara, M Watanabe, S Yamamoto, Y Shimada, Y Moriya, S	ASCO 2014	2014.5	国外
ISR 術後の直腸脱に対する手術療法 (口頭)	山口高史 松末亮 直原駿平 中西宏貴 菊地志織 川口清貴 佐治雅史 花田圭太 畑啓昭 成田匡大 大谷哲之 猪飼伊和夫	第69回日本大腸肛門病学会学術集会	2014.11	国内
局所進行直腸癌に対する術前化学療法の短期治療成績 (口頭)	松末亮 山口高史 直原駿平 菊地志織 中西宏貴 川口清貴 佐治雅史 花田圭太 畑啓昭 成田匡大 大谷哲之 猪飼伊和夫	第69回日本大腸肛門病学会学術集会	2014.11	国内
大腸癌同時性腹膜播種症例に対するGrade分類	能浦真吾	京都 (日本外科学会)	2014.4	国内
大腸癌同時性腹膜播種症例におけるMitomycin C (MMC) 腹腔内投与の意義ポスター	能浦真吾	横浜 (日本癌治療学会)	2014.8	国内
Significance of the resection of ovarian metastasis from colorectal cancersポスター	能浦真吾	Barcelona,Spain(European Society of COLOPROCTOLOGY)	2014.9	国外
Laparoscopic pelvic excenteration for locally advanced and recurrent rectal cancer	Miyake M, Ikeda M,Haraguchi N,Miyazaki M,Nakamori S,Hirao M,Miyamaoto A,Nishikawa K,Asaoka T,Yamamoto K,Sekimoto M	34th Annual Meeting of KSELS and 2014 International Symposium	2014 April	国外
Laparoscopic resection of advanced rectal cancer invading to prostate,seminal vesicle and corpus spongiosum	Haraguchi N, Murakami H,Miyake M,Maeda S,Yamamoto K,Hama N,Nishikawa K,Miyamoto A,Ikeda M,Hirao M,Nakamori S,Sekimoto M	14th JCK CRC symposium	2014 Sept	国外
StageⅣ大腸癌における予後因子の検討 (ポスター)	高倉有二、池田聡，漆原貴，井出隆太，築山尚史，今岡祐輝，真島宏聡，山下正博，野間翠，大原正裕，大石幸一，小橋俊彦，札場保宏，石本達郎，眞次康弘，中原英樹，板本敏行	第114日本外科学会定期学術集会	2014.4	国内
Quality control by photograph for evaluation of open (OP) and laparoscopic (LAP) colectomy with D3 resection for stage II/III colorectal cancer: Japan Clinical Oncology Group study JCOG 0404.	Nakajima K, Inomata M, et al., Japan Clinical Oncology Group.	2014 ASCO Annual Meeting	2014.5	国外
Clinical evidence of lap D3 resection for colorectal cancer.-Japanese randomized controlled trial-	Inomata M.	14th World Congress of Endoscopic Sur	2014.6	国外

2. 学会誌・雑誌等における論文掲載

掲載した論文 (発表題目)	発表者氏名	発表した場所 (学会誌・雑誌等名)	発表した時期	国内・外の別
Complications associated with postoperative adjuvant radiation therapy for advanced rectal cancer.	Komori K1, Kimura K, Kinoshita T, Sano T, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Uemura N, Kawai R, Shimizu Y.	Int Surg	2014	国外

Long-Term Survival of a Patient with Sigmoid Colon Cancer Showing Multiple Liver Metastases Treated by Performing Partial Hepatectomy, Five Years after Achieving a Complete Response via Hepatic Arterial Infusion Chemotherapy].	Osawa T, Sano T, Shimizu Y, Senda Y, Yamaura H, Inaba Y.	Gan To Kagaku Ryoho.	2014	国外
Immunonutrition before Extended Hepatectomy with Biliary Reconstruction for Hepatobiliary Malignancy	Monden K, Takahashi S, Kato Y, Gotohda N, KinoshitaT, Shibasaki H, Konishi M	Hepatogastroenterology	in press	国外
肝血管筋脂肪腫との鑑別を要した高度脂肪化を伴う単純結節周囲増殖型肝細胞癌の１例	本多正幸，加藤祐一郎、高橋進一郎、後藤田直人、小林達伺、小嶋基寛、佐原八束、小西大	日本消化器外科学会雑誌 47(10) 588-595	2014 4月	国内
肝原発神経内分泌癌の１例	大目祐介，加藤祐一郎、後藤田直人、高橋進一郎、小西大	日本臨床外科学会雑誌 75(11) 181-186	2014 11月	国内
直腸（各論）_特集 サルベージとコンバージョン一集学的治療で外科治療に求められるもの	塚田祐一郎、齋藤典男、伊藤雅昭、小林昭広、西澤雄介、	日本臨床外科学会雑誌 26 (4) 441-446	2014年1月	国内
Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: Final results of JCOG0205	Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H, Moriya Y.	European Journal of Cancer 50 2231-2240	2014年9月	国外
Long-term outcomes after intersphincteric resection for low-lying rectal cancer	Saito N, Ito M, Kobayashi A, Nishizawa Y, Kojima M, Nishizawa Y, Sugito M.	Ann Surg Oncol 21 3608-3615	2014年10月	国外
Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205.	Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H, Moriya Y.	Eur J Cancer	2014	国外
高齢者大腸癌に対する化学療法	Takiguchi N, Soda H, Tonooka T, Denda T. [Chemotherapy for elderly patients with colorectal cancer].	Nihon Rinsho.	2014	国内
Long-term monitoring of serum p53 antibody after neoadjuvant chemotherapy and surgery for esophageal adenocarcinoma: report of a case.	Shimada H, Nagata M, Cho A, Takiguchi N, Kainuma O, Soda H, Ikeda A, Nabeya Y, Yajima S, Yamamoto H, Sugiyama T, Itami M.	Surg Today	2014	国外
Pagetoid spreadを伴う肛門管癌を発症したLi-Fraumeni syndromeの1例	升田 貴仁，早田 浩明，滝口 伸浩，外岡 亨，山本 宏，宮崎 勝	日臨外会誌	2014	国内
イマチニブの長期投与後に経肛門的切除を施行した直腸GISTの1例	外岡 亨，滝口 伸浩，山本 宏，鍋谷 圭宏，池田 篤，貝沼 修，早田 浩明，趙 明浩，武藤頼彦，柳橋 浩男，高野 英子，傳田 忠道，永田 松夫	癌と化学療法	2014	国内
最新の消化器癌術前術後化学療法 大腸癌	金光幸秀、志田大、塚本俊輔	消化器外	2014.4	国内
腸癌切除可能肝転移に対する周術期化学療法	金光幸秀、志田大、塚本俊輔	消化器外	2014.6	国内
大腸癌肝転移に対する肝切除後の肝再発に対する治療戦略	塚本俊輔、大城泰平、坂本良平、田中征洋、落合大樹、志田大、金光幸秀	消化器外	2014.1	国内
Stage IV大腸癌根治的切除例の予後	金光幸秀,志田大,塚本俊輔,落合大樹	外科 77(1) 5-12	2015.1	国内
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Comparing incidence of enterocolitis after laparoscopic and open low anterior resection for stage II/III rectal cancer.	Inomata M, Kusano T, et al.	Asian J Endosc Surg. 7(3):214-21.	2014	国外

Ⅳ. 研究成果の刊行物・別冊

JJCO Japanese Journal of Clinical Oncology

Clinical Trial Note

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A Randomized Controlled Trial Comparing Laparoscopic Surgery with Open Surgery in Palliative Resection of Primary Tumor in Incurable Stage IV Colorectal Cancer: Japan Clinical Oncology Group Study JCOG 1107 (ENCORE Trial)

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A randomized controlled trial was started in Japan to evaluate the non-inferiority of overall survival of laparoscopic surgery to open surgery for palliative resection of primary tumor in incurable Stage IV colorectal cancer. Symptomatic, Stage IV colorectal cancer patients with non-curable metastasis are pre-operatively randomized to either open or laparoscopic colorectal resection. Surgeons in 56 specialized institutions will recruit 450 patients. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, the proportion of conversion from laparoscopic surgery to open surgery, the proportion of patients who fulfill the criteria of starting chemotherapy by 6 weeks after operation, intraoperative and post-operative complications, adverse events during chemotherapy and serious adverse events.

Key words: colorectal cancer – palliative resection – laparoscopic surgery – randomized controlled trial

INTRODUCTION

Laparoscopic resection has become an accepted therapeutic option for patients with curable colorectal cancer following the publication of large randomized trials confirming the safety and efficacy of these procedures to open resection (1–3). These trials showed that laparoscopic resections were associated with faster recovery, decreased morbidity, decreased pain and shorter hospital stay while maintaining similar cancer-related survival. Also the Japan Clinical Oncology Group (JCOG) has completed patient accrual of the Phase III study that confirmed short- and long-term clinical outcomes from a randomized controlled trial (RCT) to evaluate the laparoscopic (LAP) and open surgery (OP) for Stage II and III colon cancer: JCOG0404 (NCT00147134/UMIN-CTR: 000000105) (4). In ASCO 2012, safety and short-term clinical benefits of LAP for Stage II and III colon cancer were demonstrated (5).

These findings cannot necessarily be extrapolated to Stage IV patients because surgery is sometimes difficult due to tumor volume, tumor invasion and lymph node (LN) enlargement and is at high risk for complication. In addition, there is no RCT of LAP which focuses on Stage IV patients. A large-scale observational study was reported from Japan, which suggested that the efficacy and safety of LAP was comparable with those of OP (6,7). Thus, we designed a study, which investigates whether LAP is suitable for symptomatic, incurable Stage IV colorectal cancer with respect to survival and post-operative morbidity. The Protocol Review Committee of JCOG approved the protocol in November 2012, and the study was activated in January 2013. This trial was registered at the UMIN Clinical Trials Registry as UMIN000009715 (http://www.umin.ac.jp/ctr/).

PROTOCOL DIGEST OF THE JCOG 1107

Purpose

To confirm the non-inferiority of laparoscopic primary tumor resection in terms of overall survival compared with open resection for symptomatic incurable colorectal cancer.

Study Setting

A multi-institutional randomized Phase III trial.

Resources

This study was supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19, and 26-A-4), Grants-in-Aid for Cancer Research (24S-5 and 24S-6), and Health and Labour Sciences Research Grants for Clinical Cancer Research (H24-05) from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint is the overall survival which is measured from the date of randomization to the date of death from any cause, and it is censored at the last day when the patient is alive. Secondary endpoints are progression-free survival (PFS), the proportion of conversion from LAP to OP, the proportion of patients who fulfill the criteria of starting chemotherapy by 6 weeks after operation, intraoperative and post-operative complication, adverse events during chemotherapy and serious adverse events. PFS is measured from the date of randomization to the date of progression or death from any cause which is earlier, and it is censored at the last day when the patient is alive without any evidence of progression. When the skin incision is longer than 8 cm due to any cause, they are defined as conversion from LAP to OP. Operative complications and adverse events are recorded in accordance with Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Eligibility Criteria

Inclusion criteria

For inclusion in this study, patients must fulfill the following requirements pre-operatively: (1) pathologically proven adenocarcinoma or adenosquamous carcinoma; (2) primary tumor located at the cecum, ascending, transverse, descending, sigmoid and rectosigmoid; (3) primary tumor with bowel stenosis (no obstruction: one or more factors of the following four are fulfilled; (i) impossibility of oral intake, (ii) no flatus, (iii) abdominal distension and (iv) abnormal intestinal gas in the abdominal X-ray image) and/or bleeding (Hb < 9.0 or blood transfusion within 4 weeks before registration). If an emergency operation is needed, the patient is ineligible; (4) having at least one to three incurable factors among the following four factors: (a) hepatic metastases with the predicted remnant functional parenchyma of $<30\%$; (b) pulmonary metastases meeting any of the followings: (i) invasion suspected to the mediastinum, heart, large vessels, trachea, esophagus, vertebral body or tracheal bifurcation; (ii) predicted post-operative lung function (%FEV1.0) of $<40\%$; (iii) requiring total pneumonectomy for removal of all metastatic tumors; (iv) malignant pleural effusion or pleural dissemination; (c) distant LN metastases with 10 mm or greater short axis which fulfill any of the followings by computed tomography (CT) scan: (i) LN enlargement located above the lower edge of renal vein; (ii) LN enlargement along the common hepatic artery or the hepatoduodenal ligament with hepatic metastases; (iii) mediastinal or hilar LN enlargement with pulmonary metastases; (d) peritoneal metastases meeting any of the followings: (i) multiple irregularities or strictures of the intestinal walls confirmed by imaging; (ii) peritoneal tumor above the transverse colon; (5) no apparent invasion to adjacent organs; (6) no ascites above the pelvic cavity; (7) neither bone metastases nor brain metastases; (8) no history of abdominal surgery except gynecologic surgery for benign tumor, appendectomy and cholecystectomy; (9) PS of 0, 1 or 2; (10) aged 20–74 years old; (11) no prior treatment of chemotherapy or radiation therapy against any other malignancies, including colorectal cancer; (12) adequate organ functions and (13) written informed consent.

Exclusion criteria

(1) Synchronous or metachronous (within 5 years) malignancies other than carcinoma *in situ* or mucosal carcinoma; (2) active infectious disease requiring systemic therapy; (3) hepatitis B surface antigen positive; (4) body temperature $\geq 38°C$; (5) women during pregnancy, possible pregnancy or breast-feeding; (6) severe mental disease; (7) currently treated with systemic steroids; (8) interstitial pneumonia, pulmonary fibrosis or severe emphysema; (9) uncontrollable diabetes mellitus or routine administration of insulin; (10) uncontrolled hypertension, defined as a systolic pressure ≥ 150 and/or a diastolic pressure ≥ 100 mmHg; (11) New York Heart Association Class III/IV cardiac disease or congestive heart failure that

would take medication in order to prevent lethal ventricular arrhythmias; (12) gastrointestinal fistula, perforation or abscess within 6 months; (13) unstable angina pectoris, previous myocardial infarction or arterial thrombotic event within 6 months; (14) abdominal aortic aneurysm ($\geq$5 cm), thoracic aortic aneurysm ($\geq$6 cm) or aortic dissection; (15) congenital hemorrhagic diathesis, coagulation disorder or significant episodes of acute bleeding of Grade 3 or more according to CTCAE ver. 4.0 within the past 28 days and (16) episodes of hemoptysis within 28 days.

Randomization

After confirmation of the inclusion/exclusion criteria by telephone, fax or web-based system to the JCOG Data Center, the patients are randomized by the minimization method with balancing the arm according to ECOG PS (0 vs. 1 vs. 2) and institution.

Quality Control of Surgery

To control the quality of the operation, we limit the operator to accredited surgeons. All operations are done or directly supervised by surgeons who are certified by the Study Chair. In the OP arm, the experience of at least 30 cases of OP is needed to be certificated as an accredited surgeon. In the LAP arm, the experience of at least 30 cases of both open and laparoscopic surgeries and the board certification by the Japanese Society for Endoscopic Surgery are needed.

TREATMENT METHOD

Surgery

In both the arms, palliative resection of the primary tumor is performed. Systematic LN dissection is not allowed and minimal LN dissection to ligate feeding arteries is performed. If severe invasion to the adjacent organ is found out, resection of the invaded region is not allowed. Only slight invasion to the mesentery, small intestine, omentum, ovary, bladder, uterus or abdominal wall is allowed to be resected. Minor surgeries for benign disease such as cholecystectomy, hernia operation, etc. are acceptable. In the LAP arm, pneumoperitoneal and intracorporeal approaches are used to explore the abdomen, mobilize the colon, identify critical structures and ligate the vascular pedicle. Mobilization of the colon and identification of critical structures are performed by the pneumoperitoneal approach only. Resection of the colon, ligation of the vascular pedicle and reconstruction are performed by the pneumoperitoneal approach or the intracorporeal approach via a small incision ($\leq$8 cm). A hand-assisted LAP is permitted, but sliding window and moving window methods are not permitted.

Chemotherapy

In the all cases, post-operative chemotherapy (mFOLFOX6 plus bevacizumab, bevacizumab 5 mg/kg on Day 1, L-leucovorin 200 mg/m^2 and oxaliplatin 85 mg/m^2 as a 2 h infusion on Day 1, 5-FU 400 mg/m^2 bolus on Day 1 followed by 2400 mg/m^2 over 46 h, repeated every 2 weeks) are administered between 29 and 56 days from the surgery. If patients fulfill any of the following criteria such as having a history of hypertensive crisis or hypertensive encephalopathy, having a history of surgery or serious trauma within 28 days, having a history of intervention including a needle biopsy or having a serious and unhealed wound, mFOLFOX6 without bevacizumab is administered.

Follow-up

All patients are followed up every 8 weeks after discharge from hospital until disease progression. Blood tests including tumor markers and enhanced chest/abdominal CT are carried out at each visit.

Study Design and Statistical Method

This trial is designed to evaluate the non-inferiority of LAP to standard OP in terms of overall survival. Other endpoints, such as intraoperative and post-operative complications and the proportion of patients who fulfill the criteria of starting chemotherapy by 6 weeks after operation, are set to evaluate less invasiveness of LAP. If the non-inferiority of LAP is confirmed with statistical significance in terms of overall survival and the superiority of LAP in terms of the other endpoints as shown above, LAP will be the preferred treatment. This trial was designed to achieve at least 70% power to confirm the non-inferiority of LAP with a non-inferiority margin of 1.25 in terms of hazard ratio, and this corresponds to 4 months to the median survival time of 20 months in the both arms and a one-sided alpha of 0.05. The planed sample size was 450 patients by Schoenfeld and Richter's methods (8) with 3 years accrual and 4-year follow-up.

Interim Analysis and Monitoring

Interim analysis is planned to take place twice, taking multiplicity into account by the Lan–DeMets method with O'Brien and Fleming type boundaries. The JCOG Data and Safety Monitoring Committee (DSMC) will independently review the interim analysis report and consider stopping the trial early. In-house interim monitoring will be performed by the Data Center to ensure data submission, data quality and study progress. The monitoring reports will be submitted to and reviewed by the CCSG every 6 months.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Sapporo-Kosei General Hospital, Iwate Medical University, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, Jichi Medical School,

Saitama Medical University International Medical Center, National Cancer Center Hospital East, Chiba Cancer Center, Juntendo University Urayasu Hospital, National Cancer Center Hospital, Kyorin University School of Medicine, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Keio University Hospital, Tokyo Medical and Dental University Hospital, Toho University School of Medicine Ohashi Hospital, Kitasato University East Hospital, Kanagawa Cancer Center, Kitasato University School of Medicine, Showa University Northern Yokohama Hospital, Yokohama City University Medical Center, Saiseikai Yokohamashi Nanbu Hospital, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Ishikawa Prefectural Central Hospital, Nagano Municipal Hospital, Gifu University School of Medicine, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Fujita Health University, National Hospital Organization Kyoto Medical Center, Osaka University Faculty of Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka General Medical Center, Osaka City General Hospital, Osaka Medical College, Minoh City Hospital, Suita Municipal Hospital, Kansai Rosai Hospital, Hyogo College Of Medicine, Sano Hospital, Shimane University Faculty of Medicine, Okayama Saiseikai General Hospital, Hiroshima Prefectural Hospital, Hiroshima City Asa Hospital, Hiroshima City Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Sciences Center, Kurume University School of Medicine, Kumamoto University School of Medicine and Oita University Hospitals.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Comparing incidence of enterocolitis after laparoscopic and open low anterior resection for stage II/III rectal cancer

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Keywords
Enterocolitis; laparoscopic surgery; rectal cancer

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Abstract

Introduction: We recently observed an increased incidence of severe enterocolitis following laparoscopic low anterior resection (LAR) in some patients with stage II/III rectal cancer. This study aimed to examine the influence of laparoscopic LAR on postoperative enterocolitis compared with open LAR for Stage II/III rectal cancer.

Methods: From April 2002 to March 2012, we evaluated 65 patients with stage II/III cancer of the upper or lower rectum who underwent LAR. Among these, 27 patients underwent open LAR and 38 underwent laparoscopic LAR. First, we compared short-term outcomes between the two groups. Next, we evaluated the incidence of postoperative enterocolitis in the laparoscopic LAR group. The clinicopathological factors were examined by univariate and odds ratio (OR) analysis.

Results: Univariate analysis revealed significant differences in the occupancy rate, tumor location, depth of tumor invasion, operative time, amount of intraoperative blood loss, and postoperative enterocolitis between the laparoscopic and open groups. Postoperative enterocolitis developed in 6 of 38 patients (15.8%) in the laparoscopic group and in no patient in the open group. The occurrence of postoperative enterocolitis was significantly associated with BMI (≥28 kg/m^2), operative time, and wound infection in the laparoscopic LAR group (OR: 0.11, 95% confidence interval: 0.044–0.280, $P < 0.05$; OR: 1.40, 95% confidence interval: 1.068–1.835, $P < 0.05$; and OR: 15.0, 95% confidence interval, 1.752–128.310, $P < 0.05$, respectively).

Conclusion: Postoperative enterocolitis occurred more frequently after laparoscopic LAR than after open LAR in patients with stage II/III rectal cancer. Clinical management in the perioperative period of laparoscopic LAR is necessary to prevent postoperative enterocolitis in obese patients and those with a prolonged operative time.

Introduction

The use of laparoscopic surgery for colorectal cancer has become widespread because of its minimal invasiveness. According to the 11th Nationwide Survey of Endoscopic Surgery performed by the Japan Society for Endoscopic Surgery, 16 417 patients with colorectal cancer underwent laparoscopic surgery in 2011 (1). Laparoscopic surgery for colon cancer is recognized as a standard therapeutic modality, and the indications of this procedure for rectal cancer have been gradually expanded.

Some studies have reported no significant differences in short-term and long-term outcomes between laparoscopic and open surgery for colon cancer (2–5). With regard to rectal cancer, some studies have reported that the complication rate after laparoscopic surgery is similar

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to that after open surgery and that there is no compromise in oncological outcomes with the former (6–8). However, the complication rate with laparoscopic surgery is reportedly higher for rectal cancer than for colon cancer (9). According to a report by McKay *et al.*, the anastomotic leakage rate after laparoscopic surgery for rectal and colon cancer was 5.1% and 1.2%, respectively, while the intra-abdominal abscess rate was 6.4% and 0.9%, respectively (9). Additionally, Yamamoto *et al.* also reported that the anastomotic leakage rate in patients with stage 0/I rectal cancer who underwent laparoscopic anterior resection was 8.3% (10).

We recently observed the development of severe enterocolitis in some patients who underwent laparoscopic low anterior resection (LAR) for stage II/III rectal cancer. However, the frequency of postoperative enterocolitis is not mentioned in the 11th Nationwide Survey of Endoscopic Surgery performed by the Japanese Society for Endoscopic Surgery. In addition, no reports on severe enterocolitis in patients who have undergone laparoscopic LAR for rectal cancer are available. We reported the development of transient liver dysfunction in patients who underwent laparoscopic gastrectomy under CO_2 pneumoperitoneum, and three patients who underwent laparoscopic gastrectomy among a cohort of 27 patients with liver disease suffered severe enteritis (11). It has been hypothesized that mesenteric hypoxia and related gut ischemia–reperfusion injury, which occur during and after pneumoperitoneum, pose a significant clinical problem (12). However, only a few clinical reports of oxidative stress from laparoscopic surgery exist (11,13).

In this study, we examined the rate of postoperative ischemia-related complications, including enterocolitis after laparoscopic LAR, and compared it with the rate after open LAR in patients with stage II/III rectal cancer. In addition, we examined whether laparoscopic LAR influences the development of postoperative enterocolitis in patients with stage II/III rectal cancer.

Materials and Methods

From April 2002 to March 2012, 252 patients with rectal cancer underwent initial surgery at the Department of Gastroenterological and Pediatric Surgery, Oita University Faculty of Medicine (Oita, Japan). We excluded patients with distant metastasis and those who underwent abdominoperineal resection because of the absence of anastomosis. In Japan, D3 lymphadenectomy is defined as the dissection of the inferior mesenteric artery lymph nodes and lateral pelvic lymph nodes. We also excluded patients with preoperatively diagnosed lateral pelvic lymph node enlargement because they required lateral pelvic lymph node dissection. Therefore, we selected 65 patients with stage II/III cancer of the upper or lower rectum who required LAR with total mesorectal excision or tumor-specific mesorectal excision with inferior mesenteric artery lymph node dissection. Cancer stage was assessed according to the seventh edition of the UICC-TNM Classification of Malignant Tumors.

In our institution, we have been performing laparoscopic LAR for advanced rectal cancer since 2007. Therefore, in this study, open LAR was performed for advanced rectal cancer from 2002 to 2006. For advanced rectal cancer with invasion to other organs (T4b), we have performed open LAR since 2007. During the procedure, pneumoperitoneum was induced and maintained under 10-mmHg CO_2. The left colic artery was preserved during both laparoscopic and open LAR. Anastomosis was achieved by the double stapling technique or hand-sewn when the patient required super-LAR. We also introduced a clinical pathway during surgery for colorectal cancer at our institution: protocol, patients were preoperatively prepared according to the Guideline for Prevention of Surgical Site Infection, 1999 (14). All patients were asked to take polyethylene glycol, neomycin, and erythromycin on the day before surgery. Cefmetazole, an antibiotic, was administered on the day of surgery.

In this study, six patients were treated by preoperative chemoradiotherapy (CRT). Preoperative CRT was selected according to several preoperative sequential treatment protocols developed at our institute between 2001 and 2012. This involved the TS-1 chemotherapy regimen, which includes tegafur, gimeracil, and oteracil potassium (80 mg/m^2/day), and five fractions of radiotherapy (45 Gy at the rate of 1.8 Gy/day) every week. Our criteria for preoperative CRT was advanced rectal cancer pathologically diagnosed as adenocarcinoma and preoperatively diagnosed as T3/T4, N0-3 cancer. Primary tumor and nodal staging before and after CRT was performed using pelvic MRI and CT. Lymph nodes measuring 10 mm in diameter were considered to be metastases. If metastatic lateral pelvic lymph nodes could not be detected, lateral pelvic lymph node dissection was not performed. After surgery, the patients were examined at follow-up visits conducted every 3 months for the first 2 years and every 6 months thereafter.

At each follow-up visit, carcinoembryonic antigen and CA19-9 levels were determined. Thoracoabdominal and pelvic CT or abdominal ultrasonography was performed alternately every 3–6 months. Colonoscopy was performed annually.

We first divided the patients into two groups according to surgical procedure: the open group ($n = 27$) and the laparoscopic group ($n = 38$). Age and sex of the patients,

tumor location, tumor size, histological type, depth of tumor invasion, extent of lymphatic and vascular tumor invasion, number of positive lymph nodes, operative time, and amount of intraoperative blood loss were reviewed from the patients' surgical and pathological records. These clinicopathological characteristics and the short-term outcomes of LAR were compared between the open and laparoscopic groups. The pathological characteristics of patients in the open and laparoscopic groups were compared using the Fisher's exact test or Mann–Whitney *U*-test.

Next, we focused on the incidence of enterocolitis after surgery. Postoperative enterocolitis was defined using the Common Terminology Criteria for Adverse Events version 4.0. Because severe enterocolitis occurred only after laparoscopic LAR, patients were divided into two groups according to the absence ($n = 32$) or presence ($n = 6$) of this complication (grade 3 or higher). Similarly, the pathological characteristics of patients in these two groups were compared using the Fisher's exact test or Mann–Whitney *U*-test. The Wilcoxon rank test was used to compare median age, size of tumor, operative time, amount of intraoperative blood loss, and postoperative hospitalization duration among groups. Variables with *P*-values less than 0.05 in univariate analysis were included in odds ratios and corresponding 95% confidence intervals (CI). A *P*-value greater than 0.05 was considered statistically significant for all analyses.

All statistical analyses were performed using the SPSS 11.0 statistical software program for Windows (SPSS Inc., Chicago, USA). This study was conducted according to the Ethical Guidelines for Clinical Studies of Oita University Faculty of Medicine.

Table 1 Clinicopathological features of patients who underwent low anterior resection for stage II/III rectal cancer

Patient demography	Open ($n = 27$)	Laparoscopy ($n = 38$)	*P*-value
Sex (*n*)			0.918
Male	16 (59.3%)	23 (60.5%)	
Female	11 (40.7%)	15 (39.5%)	
Age (years)			0.370
Median	67	64.5	
Range	26–85	32–82	
BMI (kg/m^2)			0.190
<28	23 (85.2%)	36 (94.7%)	
≥28	4 (14.8%)	2 (5.3%)	
Size of tumor (mm)			0.344
Median	55	45.5	
Range	30–120	20–90	
Circumferential occupying rate (*n*)			
<50%	1 (3.7%)	14 (36.8%)	0.002
≥50%	26 (96.3%)	24 (63.2%)	
Preoperative CRT (*n*)			
Performed	1 (3.7%)	5 (13.2%)	0.412
Not performed	26 (96.3%)	33 (86.8%)	
Location (*n*)			
Upper	22 (81.5%)	20 (52.6%)	0.017
Lower	5 (18.5%)	18 (47.4%)	
T (*n*)			
T3	16 (59.3%)	34 (89.5%)	<0.01
T4	11 (40.7%)	4 (10.5%)	
N (*n*)			
N0	10 (37.0%)	19 (50.0%)	0.633
N1	11 (40.7%)	10 (26.3%)	
N2	5 (18.5%)	8 (21.1%)	
N3	1 (3.7%)	1 (2.6%)	
Stage (*n*)			
Stage II	10 (37.0%)	19 (50.0%)	0.544
Stage III A	10 (37.0%)	10 (26.3%)	
Stage III B	7 (26.0%)	9 (23.7%)	

CRT, chemoradiation therapy.

Results

In this study, all 65 patients with stage II/III rectal cancer underwent curative LAR. Univariate analysis revealed that the occupancy rate, tumor location, and depth of tumor invasion were significantly different between the open and laparoscopic LAR groups ($P < 0.05$) (Table 1). In addition, there were significant differences in the operative time, amount of intraoperative blood loss, and incidence of enterocolitis between the open and laparoscopic LAR groups ($P < 0.05$) (Table 2). Postoperative enterocolitis occurred in six patients (five men, one woman; median age, 74.5 years; interquartile range [IQR], 61.2–78.7 years; mean BMI, 26.3 ± 8.09 kg/m^2) in the laparoscopic LAR group. The clinicopathological features and short-term outcomes of the six patients with postoperative enterocolitis are shown in Table 3. The median onset period of enterocolitis was 3 days after surgery, and all six patients developed grade 3 postoperative enterocolitis. The median operative time and amount of intra-operative blood loss of patients with postoperative enterocolitis were 405 min (IQR, 362.7–470.7 min) and 185 mL (IQR, 142.5–205.0 mL), respectively. The median tumor size was 44 cm (IQR, 39.0–61.7 cm) and the median length of hospitalization was 27 days (IQR, 23.5–71.0 days). The incidence of wound infection was 50% (3/6). Regarding clinical data such as fever, white blood cell count, and C-reactive protein (CRP), the median fever was 38.8°C (IQR, 38.3–39.2°C). The median white blood cell count was 7945/mm^3 (IQR, 6572–9040/mm^3) and the median C-reactive protein was 15.6 mg/L (IQR, 13.4–23.1 mg/L).

In the laparoscopic group, there were significant differences in BMI (≥28 kg/m^2), operative time, postopera-

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Table 2 Short-term outcomes of patients who underwent low anterior resection for stage II/III rectal cancer

	Open (n = 27)	Laparoscopy (n = 38)	P-value
Operative findings			
Operation			
Operative time (min)			
Median	265	352	0.01
Range	155–570	211–1340	
Intraoperative blood loss (mL)			
Median	360	155	0.015
Range	30–2800	5–2000	
Intraoperative blood transfusion (n)			
Performed	6 (22.2%)	3 (7.9%)	0.099
Not performed	21 (77.8%)	35 (92.1%)	
Anastomotic method (n)			
Stapled	25 (92.6%)	33 (86.8%)	0.461
Hand-sewn	2 (7.4%)	5 (13.2%)	
Short-term outcomes			
Postoperative course			
Length of hospitalization (day)			
Median	18	17	0.354
Range	11–58	9–92	
Operative complications (n)			
Present	6 (22.2%)	7 (18.4%)	
Leakage	0	2	0.22
Intra-abdominal abscess	1	4	0.31
Ileus	2	0	0.089
Wound infection	3	5	0.80
Neurogenic bladder	4	1	0.07
Enterocolitis	0	6	0.03
Absent	21 (77.8%)	31 (81.6%)	
30-days mortality (n)			
Present	0 (0%)	0 (0%)	0.99
Absent	27 (100%)	38 (100%)	

CRT, chemoradiation therapy.

tive hospitalization, and incidence of wound infection between the absence of postoperative enterocolitis and presence of postoperative enterocolitis groups ($P < 0.05$) (Table 4). Regarding subanalysis of the laparoscopic LAR group, cases with an operative time of more than 330 min were associated with occurrence of postoperative enterocolitis ($P \leq 0.05$).

Subsequent odds ratio analysis using factors significant in univariate analysis revealed that BMI (≥ 28 kg/m^2), operative time, and incidence of wound infection were 0.111 (95%CI, 0.044–0.280, $P \leq 0.05$), 1.40 (95%CI, 1.068–1.835, $P \leq 0.05$), and 15.0 (95%CI, 1.752–128.310, $P \leq 0.05$), respectively (Table 5).

Discussion

In this study, laparoscopic surgery for rectal cancer was associated with a less intraoperative blood loss than open surgery, and the operative time in the laparoscopic group was longer than in the open group. These results are consistent with those of other reports (15,16). The incidence of postoperative enterocolitis in the laparoscopic group was higher than in the open group. The occurrence of enterocolitis after laparoscopic LAR was associated with BMI (≥ 28 kg/m^2), operative time, and wound infection. In this study, although only 15% (6/38) of patients who underwent laparoscopic LAR went on to develop enterocolitis, these patients developed severe enterocolitis of grade 3 or higher (Common Terminology Criteria for Adverse Events version 4.0). This suggests that clinical management for postoperative enterocolitis is necessary in patients who undergo laparoscopic LAR for advanced rectal cancer.

Recently, Yamamoto *et al.* reported that laparoscopic surgery can be used for safe resection of clinical stage 0/I rectal carcinoma (10). According to their report, the rate of postoperative enterocolitis was 0.25% (1/400). Evidence indicates that postoperative enterocolitis is a rare complication. For stage 0/I, which was excluded from this study, the rate of enterocolitis after open and laparoscopic LAR was 6.6% (1/15) and 2.9% (1/34), respectively (data not shown). There was no significant difference in the incidence of postoperative enterocolitis between the open and laparoscopic groups with stage 0/I rectal cancer. Interestingly, only patients who underwent laparoscopic LAR for advanced rectal cancer went on to develop enterocolitis in the present study. We therefore believe that the incidence of postoperative enterocolitis may be associated with laparoscopic procedures for patients with advanced rectal cancer.

Some studies have examined the surgical risk factors for enterocolitis. Evasovich *et al.* reported that CO_2 pneumoperitoneum increased the incidence of *Escherichia coli* bacterial translocation in a rat model (17). In clinical settings, there have been some reports of mesenteric ischemia, reduction of portal venous flow, and bowel infarction after laparoscopic surgery (18–22). During laparoscopic LAR for rectal cancer in the present study, patients were maintained in the Lloyd–Davies position. Therefore, we hypothesize that the intestine becomes congested by the decrease in portal venous flow subsequent to a rise in portal pressure and the intestine becomes susceptible to a mucosal membrane disorder. Furthermore, we hypothesize that enterocolitis is associated with prolonged pneumoperitoneum subsequent to prolonged operative time. As a result, subanalysis revealed that the cases with an operative time greater

Table 3 Clinicopathological findings of patients with postoperative enterocolitis

							Surgical outcome			Histology				
Patient	Sex	Age (years)	BMI	Location	Tumor size (mm)	Gross type	Operation method	Operative time (min)	Intraoperative blood loss (mL)	T stage	N stage	Histological type	Ly	V
1	F	78	25.2	Lower	35	2	Lap sLAR	355	100	3	0	Mod	–	–
2	M	82	23.4	Upper	46	2	Lap HAR	336	210	3	1	Pap	+	–
3	M	49	28.4	Lower	38	2	Lap sLAR	486	130	3	3	Pap	+	+
4	M	79	18.5	Lower	42	2	Lap sLAR	425	190	3	0	Mod	–	+
5	M	58	41.3	Lower	90	2	Lap sLAR	1340	2000	3	1	Mod	–	+
6	M	71	21.2	Lower	67	2	Lap LAR	386	180	3	2	Mod	+	+

	Postoperative complication			Clinical data							
Patient	Intra-abdominal abscess	Wound infection	Other complication	Bleeding	Peak of fever (°C)	Rebound tenderness	POD 3 WBC (/mm3)	POD 3 CRP (mg/L)	CD toxin	Length of hospitalization (day)	Recurrence
1	–	–	–	–	37.8	–	7600	36.6	–	23	–
2	–	+	–	–	38.3	–	6230	8.36	–	25	–
3	–	+	–	–	39.4	–	9290	12.8	–	29	–
4	+	+	+	–	39.1	–	8290	16.2	–	92	–
5	–	–	–	–	38.4	–	4510	25.4	–	14	–
6	–	–	+	–	39.2	–	12810	15.0	–	85	–

CD, clostridium difficile; CRP, C-reactive protein; F, female; HAR, high anterior resection; Lap, laparoscopic; LAR, low anterior resection; Ly, lymphatic invasion; M, male; Mod, moderately differentiated tubular adenocarcinoma; Pap, papillary adenocarcinoma; POD, postoperative day; sLAR, super low anterior resection; V, venous invasion; WBC, white blood cell.

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Table 4 Clinicopathological features and short-term outcomes of patients after laparoscopic low anterior resection for stage II/III rectal cancer with/without postoperative enterocolitis

	Enterocolitis		
	Absent (n = 32)	Present (n = 6)	P-value
Patient demography			
Sex (n)			0.219
Male	18 (56.3%)	5 (83.3%)	
Female	14 (43.8%)	1 (16.7%)	
Age (years)			0.279
Median	64	74.5	
Range	32–82	49–82	
BMI (kg/m^2)			0.021
<28	32 (100%)	4 (66.7%)	
≥28	0 (0%)	2 (33.3%)	
Size of tumor (mm)			0.384
Median	47.5	44	
Range	20–90	35–90	
Circumferential occupying rate (n)			0.401
<50%	27 (84.4%)	2 (33.3%)	
≥50%	5 (15.6%)	4 (66.7%)	
Preoperative CRT (n)			0.412
Performed	5 (15.6%)	0 (0%)	
Not performed	27 (84.4%)	6 (100%)	
Location (n)			0.069
Upper	19 (59.4%)	1 (16.7%)	
Lower	13 (40.6%)	5 (83.3%)	
T (n)			
T3	28 (87.5%)	6 (100%)	0.487
T4	4 (12.5%)	0 (0%)	
N (n)			
N0	17 (53.1%)	2 (33.3%)	0.241
N1	8 (25.0%)	2 (33.3%)	
N2	7 (21.9%)	1 (16.7%)	
N3	0 (0%)	1 (16.7%)	
Stage (n)			
Stage II	17 (53.1%)	2 (33.3%)	0.816
Stage IIIA	10 (31.3%)	2 (33.3%)	
Stage IIIB	5 (15.6%)	2 (33.3%)	
Operative findings			
Operation			
Operative time (min)			0.020
Median	332.5	405.5	
Range	210–730	336–1340	
Intraoperative blood loss (mL)			0.571
Median	125	185	
Range	5–560	100–2000	
Intraoperative blood transfusion (n)			0.412
Performed	30 (93.8%)	1 (16.7%)	
Not performed	2 (6.3%)	5 (83.3%)	
Anastomotic method (n)			
Stapled	29 (90.6%)	4 (66.7%)	0.169
Hand-sewn	3 (9.4%)	2 (33.3%)	
Short-term outcomes			
Postoperative course			
Length of postoperative hospitalization (day)			0.005
Median	15.5	27	
Range	9–67	14–92	
Operative complication (n)			
Present	4 (12.5%)	3 (50.0%)	
Leakage	2	0	0.65
Intra-abdominal abscess	3	1	0.39
Ileus	0	0	0.75
Wound infection	2	3	0.003
Neurogenic bladder	0	0	0.75
Absent	28 (87.5%)	3 (50.0%)	

CRT, chemoradiation therapy.

Table 5 Odds ratio of incidence of enterocolitis after laparoscopic low anterior resection

	Enterocolitis			
	Absent (n = 32)	Present (n = 6)	Odds ratio (95%CI)	P-value
BMI (kg/m^2)				0.021
<28	32 (100%)	4 (66.7%)	0.111 (0.044–0.280)	
≥28	0 (0%)	2 (33.3%)		
Operative time (min)				0.020
Median	332.5	405.5	1.40 (1.068–1.835)	
Range	210–730	336–1340		
Wound infection (n)	2 (6.3%)	3 (50.0%)	15.0 (1.752–128.310)	0.003

CI, confidence interval.

than 330 min were associated with the occurrence of postoperative enterocolitis ($P \leq 0.05$).

There may be several factors underlying the development of enterocolitis. Although enterocolitis is related to antibiotic-associated diarrhea or radiation, no significant differences were noted them between the open and laparoscopic groups in this study. Therefore, we investigated the possibility that postoperative enterocolitis developed because of a mucosal membrane disorder or mesenteric ischemia following prolonged pneumoperitoneum. It is known that 60%–70% of immune cells that control systemic immunity exist in the intestine and not in the lymph nodes and spleen (23–25). The gut-associated lymphoid tissue comprises immune cells in Peyer's patches in the intestine, and this tissue controls intestinal immunity (26–28). Because of mesenteric hypoxia and related gut ischemia–reperfusion injury that occurs during and after pneumoperitoneum, the intestine can become extremely susceptible to a mucosal membrane disorder, which is a risk factor for postoperative bacterial translocation. In such a setting, severe enterocolitis may be caused by either the excessive immune response or failure of the body's protection system. It makes sense that there was a significant difference in the incidence of wound infection between the absence of postoperative enterocolitis and presence of postoperative enterocolitis groups.

We generally perform laparoscopic LAR with pneumoperitoneum at 10 mmHg because pneumoperitoneum at 12–15 mmHg increases the intra-abdominal pressure above the normal portal circulation pressure (29). It has been reported that pneumoperitoneum pressure at 10–15 mmHg significantly decreased blood flow in the stomach by 40%, jejunum by 32%, liver by 39%, and colon by 44% (30). Because this study is a retrospective study, blood flow in the splanchnic vessels could not be measured. Therefore, it is necessary to examine the relationship between blood flow in the splanchnic vessels and the incidence of postoperative enterocolitis in the future.

It has been reported that the Lloyd–Davies position constitutes a risk factor for acute lower limb compartment syndrome, but the incidence of lower limb and abdominal compartment syndrome following laparoscopic colorectal surgery remains unknown (31). In contrast, the same report suggested that decreased venous return with pooling in the mesentery resulted from increased intra-abdominal pressure during laparoscopic surgery in the Lloyd–Davies position (31). Now, based on the results of this study, we try to return patients to the flat position from the Lloyd–Davies position and degas the abdomen every 2 h. Since we initiated these measures, we have not experienced a single case of postoperative enterocolitis. In the future, to elucidate the mechanisms by which postoperative enterocolitis occurs, operative time, position, and monitoring of relative perfusion will be needed. However, the number of cases of severe postoperative enterocolitis is small within a single institution, and multivariate analysis may not be available for such a study. For this reason, it will be necessary to examine severe enterocolitis after laparoscopic surgery in a multicenter study.

In conclusion, we demonstrated that the incidence of postoperative enterocolitis was higher after laparoscopic surgery than after open surgery for stage II/III rectal cancer. Clinical management in the perioperative period of laparoscopic LAR is necessary to prevent postoperative enterocolitis in obese patients and those with a prolonged operative time.

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大腸癌

Colorectal cancer

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●要旨●大腸癌の標準治療は外科的切除であり，この治療戦略をより有効にするために，術前あるいは術後に化学療法を併用することによって治療効果の強化が試みられている。Stage Ⅲ結腸癌の場合，現在欧米では，術後補助化学療法としてoxaliplatin併用レジメンが推奨されているが，国内外では，そのベースとなる手術成績や病理診断法に大きな隔たりがあるため，欧米の標準治療をそのまま本邦へ外挿することには慎重になる必要がある。切除可能肝転移の場合，補助化学療法の至適投与法は確立しておらず，肝切除周術期の補助化学療法を正当化するエビデンスは依然としてないのが現状である。進行直腸癌の場合，欧米の標準的補助療法である術前化学放射線療法でなくても，術前化学療法により良好な成績が得られる可能性が北米から報告され始めている。

● key words：大腸癌，術前補助化学療法，術後補助化学療法

はじめに

世界各国の大腸癌患者生存率を比較したデータから，本邦の成績はトップレベルであり，その主な要因は，Stageに応じた系統的リンパ節郭清と，精度の高い病理診断に加えて，大腸癌研究会によって『大腸癌取扱い規約』が提示され，根治性を重視する一貫した姿勢が保たれてきたことも背景の1つと思われる。一方，欧米では，2004年にoxaliplatin＋5-FU＋LV併用療法の有用性が示された以降は，結腸癌術後補助化学療法としてoxaliplatin併用レジメンが推奨されているが，本邦と欧米の大腸癌の5年生存率には約10%の差があり，欧米の標準治療を本邦の実地臨床にそのまま利用することには慎重さが求められる。

本稿では，現状における大腸癌に対する術前術後補助化学療法について，最新の知見に基づきながら解説する。

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結腸癌に対する術後補助化学療法

1. 欧 米

近年の大腸癌（結腸癌）に対する術後補助療法の臨床試験は主に欧米を中心に積極的に行われ，1980年代後半以降，5-FU/levamisole療法[1]や5-FU/LV療法[2]において，術後補助薬物療法の手術単独群に対する有用性が示された。

1) NSABP C-06試験

その後，NSABP C-06においては，Stage Ⅱ/Ⅲ（47%/53%）の結腸癌を対象としてbolus 5-FU/LV療法（Roswell Park Memorial Institute；RPMI regimen）とUFT/LV療法とのランダム化比較試験として行われ，無病生存期間（disease free survival；DFS），全生存期間（overall survival；OS）が同等であることが示された[3]。

2) X-ACT試験

Stage Ⅲの結腸癌を対象にcapecitabine療法とbolus 5-FU/low dose LV（Mayo regimen）療法と比較したX-ACT試験において，capecitabineは5-FU/LVと同等の効果であることが示された[4]。また，5-FU/LVの投与方法として，bolus 5-FUを主