直腸癌術後多発肝転移に対してSOX + Bevacizumab療法にてCRを得た1例

Kabashima, Akira
Department of Surgery, Munakata Medical Association Hospital

Kimura, Koichi
Department of Surgery, Munakata Medical Association Hospital

Sanefuji, Kensaku
Department of Surgery, Munakata Medical Association Hospital

Maekawa, Soichiro
Department of Surgery, Munakata Medical Association Hospital

https://doi.org/10.15017/1808303

出版情報：福岡醫學雜誌. 108 (1), pp.8-14, 2017-01-25. 福岡医学会
バージョン：
権利関係：

Case Report

Completely Responsive Multiple Liver Recurrence of Colon Cancer Treated Using Chemotherapy with Oral S-1 and Oxaliplatin Plus Bevacizumab : A Case Report

Akira Kabashima, Koichi Kimura, Kensaku Sanefuji and Soichiro Maekawa

Department of Surgery, Munakata Medical Association Hospital, 811-3431 Fukuoka, Japan

Abstract

Although chemotherapy with oral S-1 and oxaliplatin (SOX) plus bevacizumab (bev) is safe and feasible for patients with advanced or recurrent colorectal cancer, it is difficult to achieve a complete response (CR) using only chemotherapy. A 67-year-old man underwent endoscopic mucosal resection and additional sigmoidectomy (D2 dissection) for submucosal invasive sigmoid colon cancer. Multiple liver metastases were diagnosed 1.5 years later, and chemotherapy with SOX + bev was initiated. Computed tomography (CT) after the end of the third course revealed reduced liver recurrence. Liver metastases could not be identified using CT after the end of the sixth course. Grade 1 peripheral neuropathy was the only side effect of this regimen. Subsequently, the chemotherapy regimen was changed to oral S-1. CT evaluation revealed that there was no recurrence at 6 months after the regimen change.

Key words : colorectal cancer, SOX + bevacizumab, complete response

Introduction

Surgical resection is considered the treatment of choice for resectable recurrent colon cancer. Multiple-drug chemotherapy including targeted molecular therapy is the standard therapy for unresectable recurrent colon cancer. However, it is difficult to achieve a complete response (CR) only using chemotherapy. In the present study, we report a case of colon cancer recurrence in a patient who achieved a CR while maintaining good quality of life after chemotherapy with oral S-1 and oxaliplatin (SOX) plus bevacizumab (bev).

Case report

A 67-year-old man underwent endoscopic mucosal resection to sigmoid colon cancer in January 2014 (Fig. 1). The pathological diagnosis was as follows : adenocarcinoma in adenoma ; 0-Ip ; well differentiated adenocarcinoma in tubular adenoma with moderate atypia invading into the submucosa ; pSM (head invasion) ; ly1 ; v0 ; sprouting(+) ; INFalpha. The cut ends were free of neoplastic tissue. Therefore, we performed additional sigmoidectomy with D2 dissection in March 2014. Pathologically, neither remnant cancer cells nor lymph node metastasis were observed in the resected specimen. Finally, the progress was pStage I (SM, N0, H0, P0, M0). Because of leakage from the anastomosis, intraperitoneal drainage and ileostomy were performed on day 9 after the first operation. Then, the patient underwent closure of the ileostomy in July 2014. In September 2015, multiple liver

Corresponding author : Akira Kabashima. akaba@munakata-med-hp.gr.jp
Department of Surgery, Munakata Medical Association Hospital, 5-3-3 Taguma, Munakata, 811-3431 Fukuoka, Japan
Tel : 81-0940-37-1188 Fax : 81-0940-37-0016

Abbreviations : SOX : oral S-1 and oxaliplatin, bev : bevacizumab, CR : complete response, CT : computed tomography, PFS : progression free survival, 5-FU : fluorouracil, FOLFOX : folinic acid and 5-FU (either bolus or infusion) with oxaliplatin, respectively), FOLFIRI : folinic acid and 5-FU (either bolus or infusion) with irinotecan.

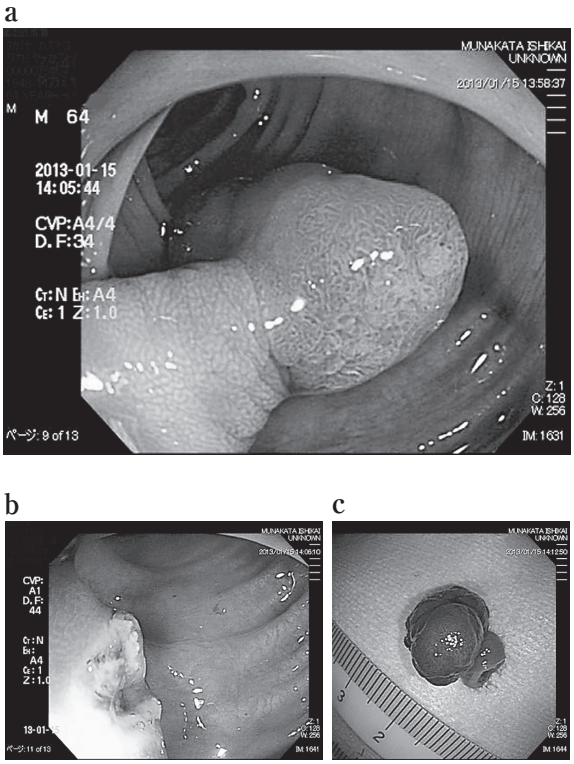

Fig. 1 **a** : Endoscopic examination revealed a 14 mm 0-Ip type polypoid lesion in the sigmoid colon located 30 cm from the anal edge. **b** and **c** : Endoscopic mucosal resection was performed.

metastases were diagnosed using computed tomography (CT) (Fig. 2a). In addition, multiple ground glass-like shadows, which were suspected multiple lung metastases, were recognized in both lungs (Fig. 2b). SOX + bev chemotherapy was initiated in October 2015. The SOX + bev regimen consisted of intravenous bevacizumab 7.5 mg/kg and oxaliplatin 130 mg/m^2 on day 1 and co-administration of oral S-1 120 mg 2x on days 1-14. This drug regimen was repeated every 3 weeks. In December 2015, CT after the end of the third course revealed a reduction in liver recurrences (Fig. 3a). No changes were recognized in the lung lesions ; inflammatory changes were suspected rather than neoplastic changes at this point (Fig. 3b). In March 2016, CT after the end of the sixth course revealed liver metastases had become impossible to identify (Fig. 3c). The only side effect during the period of treatment using this regimen was grade 1 peripheral neuropathy. There was no necessity for extension of the drug holiday and no drug-related weight loss. Subsequently, the chemotherapy regimen was changed to oral S-1 for patient-related economical reasons. CT scans in June and September 2016 did not reveal re-emergence of the lesion.

Discussion

Molecular target drugs plus FOLFOX (leucovorin, fluorouracil and oxaliplatin) or FOLFIRI (leucovorin, fluorouracil and irinotecan) are considered the first-line treatment for advanced and recurrent colorectal cancer[1)~5)]. In Japan, oral S-1 has been widely used for the treatment of gastrointestinal cancers. Several phase II studies have proved the effectiveness and safety of oral S-1 monotherapy[6)~8)]. Furthermore, several phase I or II studies have reported the efficacy and feasibility of chemotherapy with SOX (oral S-1 and oxaliplatin) as a first-line chemotherapy for metastatic colorectal cancer[9)~11)]. The SOFT trial was undertaken as an open-label, non-inferiority, randomized phase III trial in Japan[12)]. The SOFT trial reported that SOX + bev was as effective as FOLFOX6 + bev in terms of progression free survival (PFS) in patients with metastatic colorectal cancer. In addition, the SOFT trial also reported that SOX + bev was as safe as FOLFOX6 + bev.

Although chemotherapy with SOX has been considered to be efficacious as a first-line chemotherapy for advanced or recurrent colorectal cancer, there is little evidence that a CR has been achieved using this chemotherapy regimen alone. Soft study reported that 4 cases of 256 SOX + bev regimen group achieved CR[12)]. Maruo et al. reported that a CR was achieved in one case among 14 with advanced or recurrent colorectal cancer using chemotherapy with SOX + bev[13)]. But no detailed description regarding the sites of metastasis or recurrence was reported in the previous reports. Only two cases have been reported involving sites of metastasis or recurrence. Ibuki et al. reported a case of peritoneal dissemination[14)], and Yokota et al. reported a case

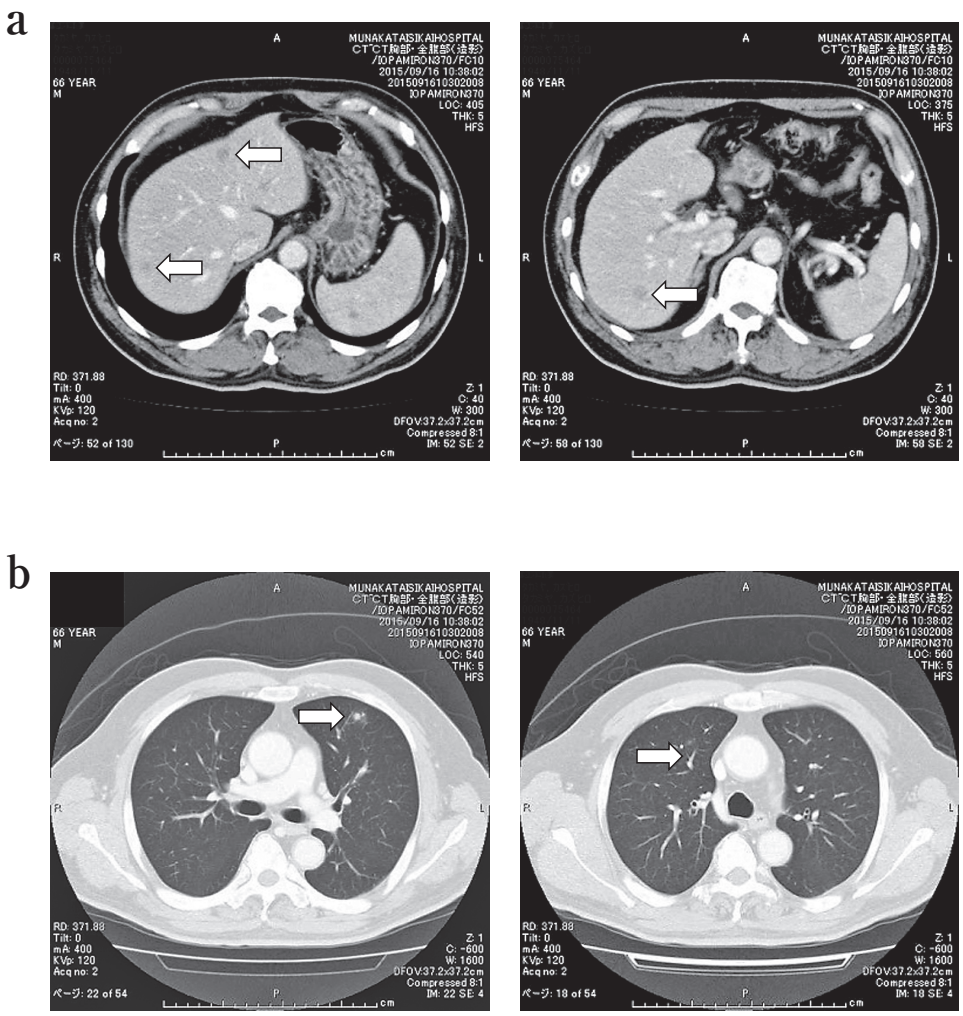

Fig. 2 Computed tomography (CT) examination carried out in September 2015. **a** : Abdominal CT images showing multiple low density areas in the liver, that were diagnosed as multiple metastases (narrow arrows). **b** : Chest CT images showing multiple ground glass-like shadows in both lungs, that were suspected of being multiple metastases (thick arrows).

of liver metastasis[15]. The present report can therefore be regarded as rare and valuable.

In our case, the chemotherapy with oral S-1 has been continued as the maintenance therapy after the achievement of a CR. The optimal duration of administration of this chemotherapy regimen after a CR has been achieved should be investigated in a future study. There have been four previous case reports involving advanced and recurrent colorectal cancer where CR was observed as a result of chemotherapy with oral S-1[15)~18)]. One of the four cases died of re-recurrence involving peritoneal dissemination[16]. In the remaining three cases, chemotherapy with oral S-1 has been continued after the achievement of a CR during the reporting period[15)17)18)]. However, the optimal chemotherapy administration period with oral S-1 after a CR has been observed remains unclear. In conclusion, we reported a rare case of recurrent colon cancer where a CR was achieved exclusively using chemotherapy with SOX + bev ; findings suggested that chemotherapy with SOX + bev is safe and feasible for patients with advanced or recurrent colorectal cancer.

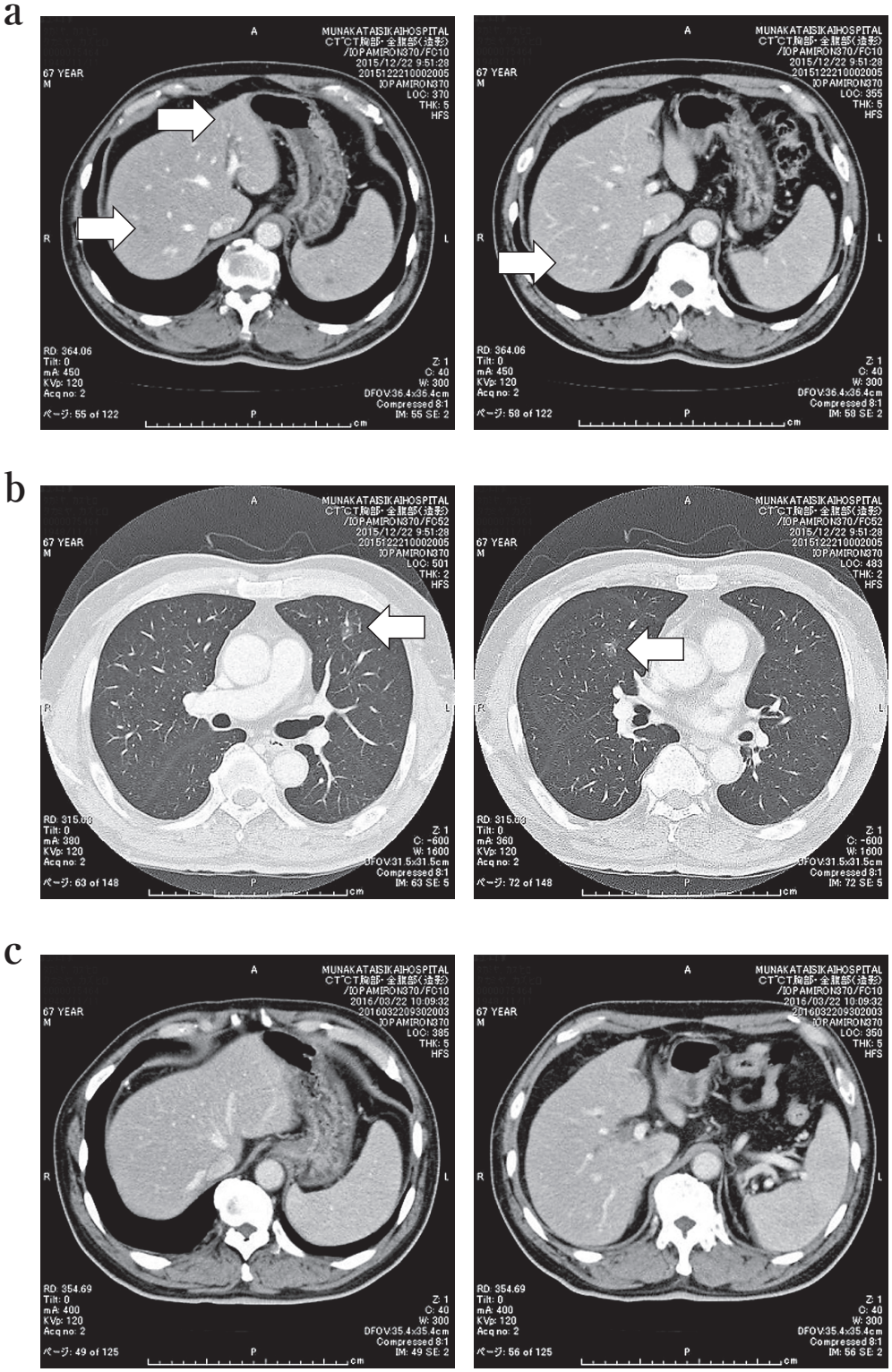

Fig. 3 Follow-up involving computed tomography (CT). **a** : Abdominal CT images acquired after the end of the third course of chemotherapy showing a reduction in liver recurrences (narrow arrows). **b** : Chest CT images acquired after the end of the third course of chemotherapy showing that the lesions in the lung had not changed (thick arrows). **c** : CT images after the end of the sixth course of chemotherapy showing that metastases in the liver had become impossible to identify.

Competing interests

The authors declare that they have no competing interests.

References

1) Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, Debraud F, Figer A, Grossmann J, Sawada N, Schöffski P, Sobrero A, Van Cutsem E and Díaz-Rubio E : XELOX (capecitabine plus oxaliplatin) : Active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol. 22 : 2084-2091, 2004.
2) de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, CortesFunes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F and Bonetti A : Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 18 : 2938-2947, 2000.
3) Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL and Lévi F : Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol. 18 : 136-147, 2000.
4) Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L and Rougier P : Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer : A multicentre randomised trial. Lancet. 355 : 1041-1047, 2000.
5) Meyerhardt JA and Mayer RJ : Systemic therapy for colorectal cancer. N Engl J Med. 352 : 476-487, 2005.
6) Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K and Taguchi T : Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. Br J Cancer. 83 : 141-145, 2000.
7) Van den Brande J, Schöffski P, Schellens JH, Roth AD, Duffaud F, Weigang-Köhler K, Reinke F, Wanders J, de Boer RF, Vermorken JB and Fumoleau P : EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. Br J Cancer. 88 : 648-653, 2003.
8) Shirao K, Ohtsu A, Takada H, Mitachi Y, Hirakawa K, Horikoshi N, Okamura T, Hirata K, Saitoh S, Isomoto H, Isomoto H and Satoh A : Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. Cancer. 100 : 2355-2361, 2004.
9) Suzuki S, Shimazaki J, Morishita K, Koike N, harada N, Hayashi T and Suzuki M : Efficacy and safety of Oxaliplatin,bevacizumab and oral S-1 for advanced recurrent colorectal cancer. Mol Clin Onco1. 5 : 391-394, 2016.
10) Zang DY, Lee BH, Park HC, Song HH, Kim HJ, Jung JY, Kim JH, Kim HY, Kwon JH, Hwang SW, Park SR, Park CH, Kim KO, Kim MJ and Jang KM : Phase II study with oxaliplatin and S-1 for patients with metastatic colorectal cancer. Ann Oncol. 20 : 892-896, 2009.
11) Yamada Y, Tahara M, Miya T, Satoh T, Shirao K, Shimada Y, Ohtsu A, Sasaki Y and Tanigawara Y : Phase I/II study of oxaliplatin with oral S-1 as FIRST-line therapy for patients with metastatic colorectal cancer. Br J Cancer. 98 : 1034-1038, 2008.
12) Yamada Y, Takahari D, Matsumoto H, Baba H, Nakamura M, Yoshida K, Yoshida M, Iwamoto S, Shimada K, Komatsu Y, Sasaki Y, Satoh T, Takahashi K, Mishima H, Muro K, Watanabe M, Sakata Y, Morita S, Shimada Y and Sugihara K : Leucovorin, fluorouracil and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT) : An open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol. 14 : 1278-1286, 2013.
13) Maruo H, Suzuki K, Ishikawa S, Murakami T, Higashi Y, Shoji T, Yamazaki M, Taniguchi M and Nishiyama R : Study of S-1 and oxaliplatin (SOX) plus bevacizumab as first-line therapy in patients with unresectable colorectal cancer. Jpn J Cancer Chemother. 41 : 2583-2586, 2014.
14) Ibuki Y, Yoshimitu M, Emi M, Mukaida H, Hirabayashi N, Kgimoto A, Kaneko M and Takiyama W : Pathological complete response to SOX plus bevacizunab for treating stage IV sigmoid colon cancer. Jpn J Cancer Chemother. 43 : 769-772, 2016.
15) Yokota T, Sano T, Shimizu Y, Takahari D, Senda Y, Shimura M, Ura T, Shitara K, Nimura Y, Yatabe Y and Muro K : Pathological complete response of colorectal liver metastases following

chemotherapy with S-1 and oxaliplatin (SOX) in combination with bevacizumab : Acase report. Oncol Lett. 2 : 201-205, 2011.
16) Kanazawa S, Seo A, Tokura N, Honda R, Kase H and Teramoto T : Liver metastasis from sigmoid colon cancer with peritoneal dissemination showed a complete response to TS-1. Jpn J Cancer Chemother. 33 : 113-117, 2006.
17) Nobuhara Y, Kubo N, Matuoka T and Yo T : Liver metastasis from sigmoid colon cancer showed a complete response to S-1 after recurrence with FOLFOX6 treatment. Jpn J Cancer Chemother. 37 : 177-179,2010.
18) Egi H, Okajima M, Takakura Y, Nakahara H, Matsugu Y, Kohashi T, Kadoya T, Ohmori I, Urushihara T and Itamoto T : A case of advanced rectal cancer that responded to S-1 with an extended complete response. Jpn J Cancer Chemother. 36 : 1911-1914, 2009.

(Received for publication January 6, 2017)

（和文抄録）

直腸癌術後多発肝転移に対して SOX + Bevacizumab 療法にて CR を得た 1 例

椛島　章，木村光一，實藤健作，前川宗一郎

宗像医師会病院　外科

【はじめに】再発大腸癌の治慮法は，切除可能であれば，手術療法が第一選択であると考えられる．それが不可能な際は分子標的薬を含めた多剤併用による化学療法を選択するのが標準と考えられるが，化学療法のみで CR を得ることは困難である．

【症例】67 歳男性．2013 年 1 月に S 状結腸癌に対して EMR を施行した．病理診断は，Adenocarcinoma in adenoma, Ip. Well differentiated adenocarcinoma in tubular adenoma with moderate atypia, invading into the submucosa, pSM(head invasion), ly1, v0, sprouting(+), INF alfa. The cut end is free of neoplastic tissue. そこで，同年 3 月に S 状結腸切除術（D2 郭清）を施行した．病理診断は，癌の遺残は認められず，最終的な進行度は SM,N0, H0, P0, M0 pStageI であった．2015 年 9 月，CT と MRI より多発肝転移が診断された．また，肺にも多発するすりガラス様陰影を認め，多発肺転移が疑われた． 2015 年 10 月より SOX + Bevacizumab 療法を開始した．Bevacizumab 7.5 mg/kg と Oxaliplatin 130 mg/m^2 を D1 に点滴投与し，S-1 120mg2x を D1-14 の 2 週間服用した．その後 1 週間休薬し，3 週間で 1 コースとした．3 コース終了後の 2015 年 12 月の CT にて肝再発巣は縮小を認めた．肺の病変は変化を認めず，腫瘍性変化より炎症性変化が疑われた．6 コース終了後の 2016 年 3 月の CT では肝の転移巣は同定不能となった．治療期間中の side effect は grade1 の末梢神経障害だけであり，休薬や薬剤減量の必要はなかった．患者の経済的な理由よりその後は TS-1 の服用に加療を変更した．2016 年 6 月と 9 月の CT では病変の再出現を認めていない．

【まとめ】今回，われわれは，SOX + Bevacizumab 療法による化学療法にて QOL を維持しながら CR を得た稀な大腸癌再発症例を経験したので報告した．

キーワード：大腸癌，再発，SOX + Bevacizumab 療法，完全寛解