nerve system was preserved completely in 18 patients and unilaterally in two; no recurrence was found in this region by repeated follow-up CT and MRI. The overall survival rate, estimated by the Kaplan–Meier method, of the 18 patients without micrometastases surrounding the pelvic plexus was 94 per cent at 1 year and 88 per cent at 3 years. Neither of the patients with micrometastases was alive at 1 year after surgery.

Discussion

The lateral ligament is still regarded as a pathway of lymphatic vessels (middle lymphatic flow) from the lower rectum towards the lateral lymph nodes[1,19]. However, in the present study micrometastases to the connective tissues, including the lateral ligament, were identified by highly sensitive RT–PCR analysis in only two patients with distant metastases. Three of five patients with both upper and lateral lymph node metastases had no micrometastases in the connective tissues. A partial explanation for the discrepancy between the presence of lymph node metastases and the very low incidence of micrometastases to the connective tissues might be that lateral lymph node metastases developed via lower lymphatic flow rather than via middle lymphatic flow through the lateral ligament[19].

The autonomic nerve system was completely preserved in all but two patients in the present study, However, no local recurrence in the region of the preserved nerve system was observed by CT and MRI during follow-up. Contrary to expectation, micrometastases to the connective tissue surrounding the pelvic plexus were rare, verifying the feasibility of nerve preservation without oncological compromise in most patients.

Neither patient with micrometastases in the tissues surrounding the pelvic plexus survived for 1 year after surgery. Ueno *et al.*[14] performed complete dissection of the autonomic nerve system and pelvic lymph nodes with the aim of achieving local control in 61 patients with rectal cancer. They reported spread of cancer cells to the autonomic nerves in nine patients (15 per cent), six with Dukes' C and three with Dukes' 'D' lesions. The patients with Dukes' C tumours underwent curative radical resection, but all developed recurrence within 1 year and none survived for 4 years. The circumferential resection margin for TME is located inside the pelvic plexus whereas the pelvic nerve plexus and the lateral tissue are situated outside the margin. It has also been documented that TME in patients with tumour involvement of circumferential resection margin is associated with a poor prognosis[20].

The present results indicate that any patients with micrometastases in the preserved pelvic plexus already have advanced cancer, so their prognosis is unlikely to be affected by local recurrence that might develop if the autonomic nerves are preserved. Management of such patients should focus on maximizing the quality of remaining life.

The follow-up period in the present study was relatively short (median 36·0 months). However, some 50–80 per cent of local recurrences occur within 2 years after rectal cancer surgery, with a peak at 6–12 months[21]. The follow-up period should therefore have been sufficient for the analysis.

Based on examination of micrometastases, these results suggest that the autonomic nerve system should be preserved wherever possible, even in surgery for advanced rectal cancer. However, study of more patients positive for micrometastases is needed.

Acknowledgements

This work was supported by a Grant-in-Aid for Cancer Research from the Ministry of Education, Science, Sports and Culture Technology, Japan.

References

1 Sauer I, Bacon HE. Influence of lateral spread of cancer of the rectum on radicability of operation and prognosis. *Am J Surg* 1951; **81**: 111–120.
2 Bernstein WC, Bernstein EF. Sexual dysfunction following radical surgery for cancer of the rectum. *Dis Colon Rectum* 1966; **9**: 328–332.
3 Lee JF, Maurer VM, Block GE. Anatomic relations of pelvic autonomic nerves to pelvic operations. *Arch Surg* 1973; **107**: 324–328.
4 Heald RJ, Ryall R. Recurrent cancer after restorative resection of the rectum. *Br. Med. J. (Clin Res Ed)* 1982; **284**: 826–827.
5 Murty M, Enker WE, Martz J. Current status of total mesorectal excision and autonomic nerve preservation in rectal cancer. *Semin Surg Oncol* 2000; **19**: 321–328.
6 Pocard M, Zinzindohoue F, Haab F, Caplin S, Parc R, Tiret E. A prospective study of sexual and urinary function before and after total mesorectal excision with autonomic nerve preservation for rectal cancer. *Surgery* 2002; **131**: 368–372.
7 Enker WE. Potency, cure, and local control in the operative treatment of rectal cancer. *Arch Surg* 1992; **127**: 1396–1401; discussion 1402.
8 Koyama Y, Moriya Y, Hojo K. Effects of extended systematic lymphadenectomy for adenocarcinoma of the rectum – significant improvement of survival rate and decrease of local recurrence. *Jpn J Clin Oncol* 1984; **14**: 623–632.
9 Matsuoka N, Moriya Y, Akasu T, Fujita S. Long-term outcome of urinary function after extended

lymphadenectomy in patients with distal rectal cancer. *Eur J Surg Oncol* 2001; **27**: 165–169.
10 Saito N, Koda K, Nobuhiro K, Takiguchi K, Oda K, Soda H *et al.* Nerve-sparing surgery for advanced rectal cancer patients: special reference to Dukes C patients. *World J Surg* 1999; **23**: 1062–1068.
11 Mori T, Takahashi K, Yasuno M. Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal cancer surgery and its results: the impact of lateral lymph node dissection. *Langenbecks Arch Surg* 1998; **383**: 409–415.
12 Maas CP, Moriya Y, Steup WH, Kiebert GM, Kranenbarg WM, van de Velde CJ. Radical and nerve-preserving surgery for rectal cancer in The Netherlands: a prospective study on morbidity and functional outcome. *Br J Surg* 1998; **85**: 92–97.
13 Yamakoshi H, Ike H, Oki S, Hara M, Shimada H. Metastasis of rectal cancer to lymph nodes and tissues around the autonomic nerves spared for urinary and sexual function. *Dis Colon Rectum* 1997; **40**: 1079–1084.
14 Ueno H, Mochizuki H, Fujimoto H, Hase K, Ichikura T. Autonomic nerve plexus involvement and prognosis in patients with rectal cancer. *Br J Surg* 2000; **87**: 92–96.
15 Miyake Y, Yamamoto H, Fujiwara Y, Ohue M, Sugita Y, Tomita N *et al.* Extensive micrometastases to lymph nodes as a marker for rapid recurrence of colorectal cancer: a study of lymphatic mapping. *Clin Cancer Res* 2001; **7**: 1350–1357.
16 Noura S, Yamamoto H, Ohnishi T, Masuda N, Matsumoto T, Takayama O *et al.* Comparative detection of lymph node micrometastases of stage II colorectal cancer by reverse transcriptase polymerase chain reaction and immunohistochemistry. *J Clin Oncol* 2002; **20**: 4232–4241.
17 Sobin LH, Wittekind C (eds). *UICC: TNM Classification of Malignant Tumours* (6th edn). Wiley-Liss: New York, 2002.
18 Chomczynski P, Sacchi N. Single-step method of RNA isolation by acid guanidinium thiocyanate–phenol–chloroform extraction. *Anal Biochem* 1987; **162**: 156–159.
19 Takahashi T, Ueno M, Azekura K, Ohta H. Lateral ligament: its anatomy and clinical importance. *Semin Surg Oncol* 2000; **19**: 386–395.
20 Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP *et al.* Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002; **235**: 449–457.
21 Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**: 638–646.

早期大腸癌 2004 Vol.8 No.6

IV 新しい検診法の可能性
(2) PET

山口 茂樹* 古川 敬芳** 森田 浩文*
石井 正之* 大田 貢由*

I. FDG-PETとは

PET(positron emission tomography)はポジトロンによる断層撮影で，1970年代に実用的装置の開発，FDG(2-deoxy-2-^{18}F-fluolo-D-glucose；^{18}FDG)の合成がなされた．FDGはD-glucoseと同様に細胞内に取り込まれリン酸化されるが，D-glucoseのように速やかに水と二酸化炭素には分解されず細胞や組織内に蓄積する．したがって糖代謝の盛んな細胞に集積する．このFDGをPETカメラで撮影し集積部位を診断するのがPET検査である．はじめFDGは脳代謝の研究に使用されたが，1980年代に腫瘍へも応用された．2002年には癌にも保険適応され，再発部位不明大腸癌，質的診断として良性悪性の鑑別，腫瘍のバイアビリティ評価(治療効果判定)などに有効である．

これまでの画像診断とまったく異なる点は，たとえばCTではX線透過性を，MRIでは磁気を利用して形態診断を行うが，FDG-PETではglucose代謝を利用して細胞の機能から異常部位の診断を行うことである．したがってまったく新しい原理の検査法として期待も大きい．

しかしながらFDG-PETを行うためには^{18}Fを製造するサイクロトロン(ポジトロン放出核種^{18}Fの物理学的半減期は110分と短いため)，FDG合成装置，PETカメラ(図1)が必要である．導入のために莫大な経費がかかるため保有施設は限られる．また核医学検査は高価な検査で，検診利用では全額自費となるため受診者の負担も大きい．また現在，院内で製造されるFDGは薬事法の規制を受けないため，各施設が薬剤の衛生管理，品質管理について責任をもつことを要求されるなど大変手間もかかる．

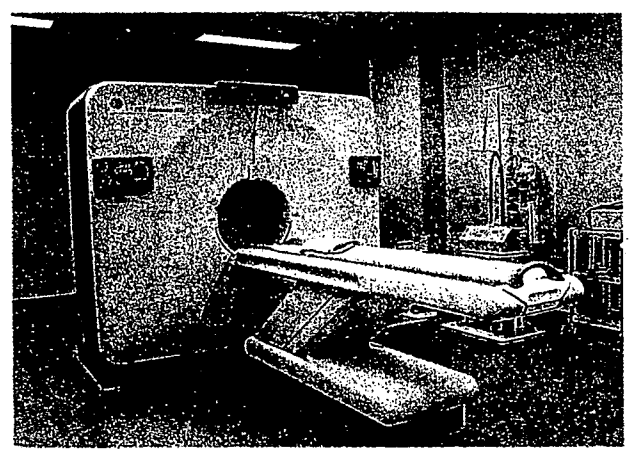


図1 PET撮影装置

*静岡県立静岡がんセンター大腸外科 **同 画像診断科
(〒411-8777 静岡県駿東郡長泉町下長窪1007)

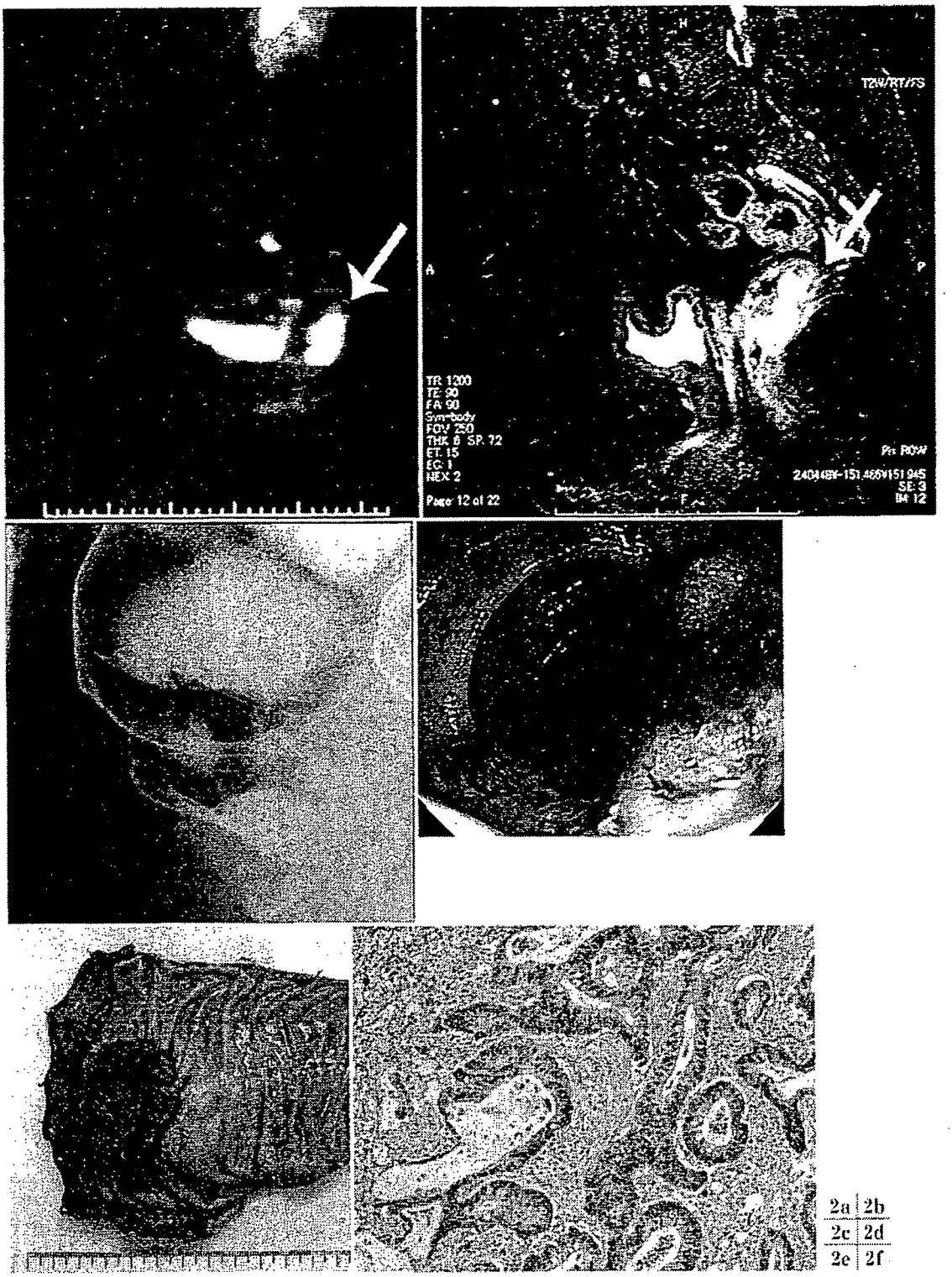
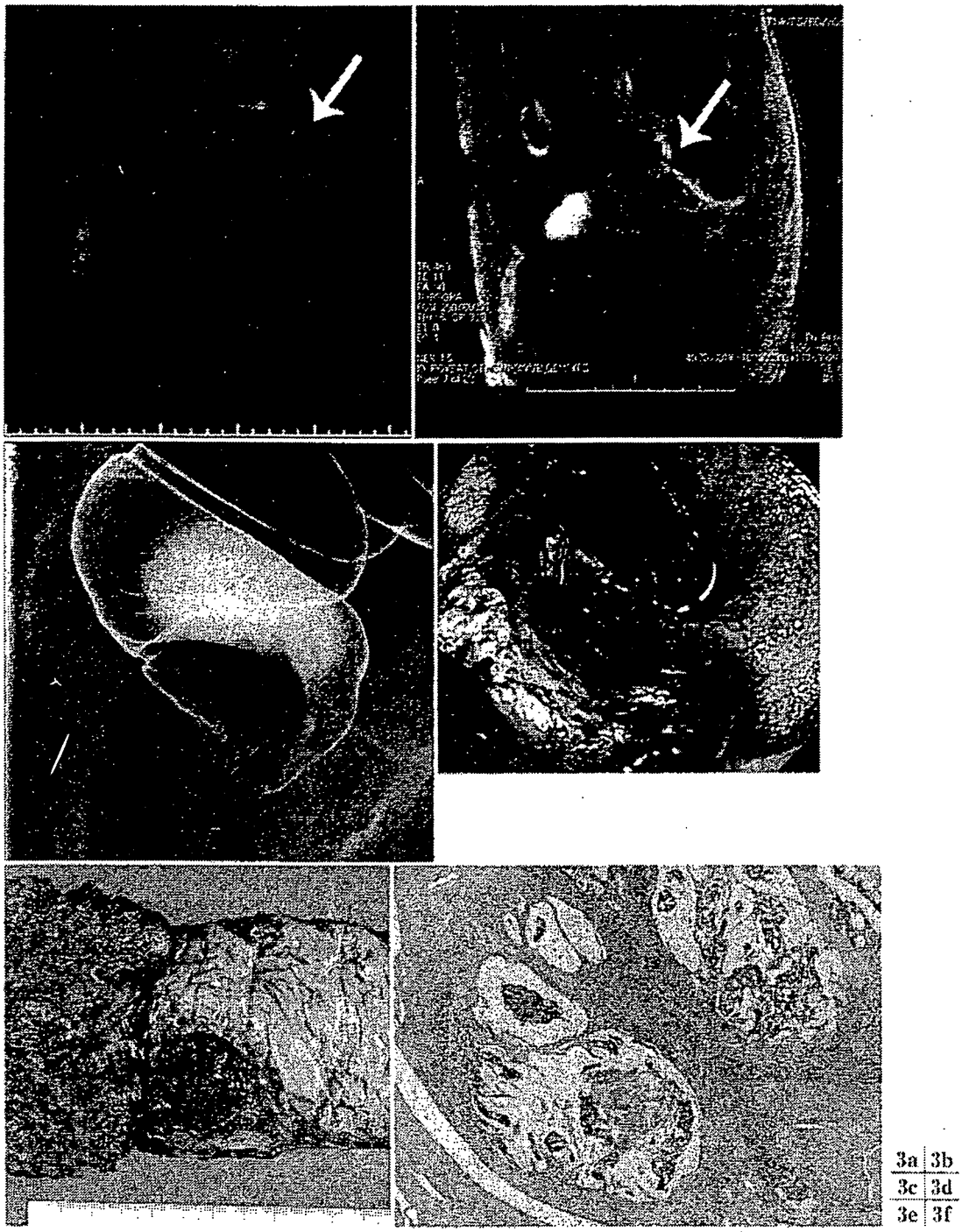


図2　直腸癌症例のFDG-PET

a：FDG-PET矢状断．膀胱の生理的集積の背側に著明な集積を認める．
b：MRI矢状断．下部直腸の進行癌を認める．
c：注腸X線像
d：内視鏡像
e：切除標本肉眼像
f：病理組織像(×10)



3a | 3b
3c | 3d
3e | 3f

図3　直腸癌側方リンパ節転移症例のFDG-PET
a：FDG-PET 矢状断．骨盤壁に異常な集積を認める．
b：MRI 矢状断．内腸骨領域に2 cm 大の転移リンパ節を認める．
c：注腸X線像
d：内視鏡像
e：切除標本肉眼像
f：病理組織像

II. FDG-PETによるがん検診

現在のがん検診は胃，大腸，肺，乳腺など臓器別に行われている．FDG-PETの特徴は，前処置を含め苦痛がない，標的臓器がない(一度にほぼ全臓器が対象となる)，存在診断とともに転移についても診断が可能などである．

実際のがん検診への利用は1994年の山中湖クリニックに始まる．井出の報告[1]によると，1994～2003年に7,793人の受診で104人(1.3％)のFDG-PET陽性癌を発見し，その内訳は腺腫内癌を含む大腸癌24人，肺癌22人，甲状腺癌21人，乳癌12人，胃癌6人などとなっている．一方，同時期に併用検査にて100人(1.28％)とほぼ同数のFDG-PET陰性癌も発見しており，内訳と検査法は前立腺癌29人(PSA)，肺癌12人(ヘリカルCT)，大腸癌8人(便潜血，このうち6人は腺腫内癌)，膀胱癌8人(US，MRI)，胃癌4人(US，HP)などである．

FDG-PETは検診として万能ではないため，ほかの検査の併用を必要としている．しかしながらFDG-PET陽性癌発見率1.3％の数字は，一般のがんドックでの発見率に勝っている．本邦における高齢化社会の進行，癌死亡数の増加を考えれば，身体への負担が少なく全身を検診できその検出率が高いことから，今後期待される方法の一つといえる．

III. 大腸癌検診としてのPET(図2, 3)

宇野らの報告[2]によると，2000年から3年間の約8,000例のFDG-PET検診で1.71％の癌を発見し，上位は甲状腺，肺，大腸，乳腺の順で70％がFDG-PET陽性癌だった．このうち大腸癌は90％近くがFDG-PET陽性で，進行度はstage 0(粘膜内癌)20％，stage I 14％，stage II 47％だった．一部の症例では便潜血陰性のものをFDG-PETで検出できた．高い陽性率から今後，FDG-PETが大腸癌検診として有力な武器になる可能性が示唆されている[3]．

参考までに平成14年度静岡県大腸がん地域検診の報告[4]では，検診対象者数816,341人，受診者数210,858人(25.8％)，要精検者数14,047人(要精検率6.7％)，精検受診者7,812人(精検受診率55.6％)で，精検方法の80％が大腸内視鏡検査だった．癌発見者272人，ポリープ発見者2,581人であり，受診者に対する大腸癌発見率は0.13％，ポリープ発見率1.2％だった．静岡県の受診率は全国平均の約15％より10％ほど高くなっているが，大腸癌発見率は約0.1％で，便潜血＋大腸内視鏡による精検の限界と思われる．これを年齢階層別にみると40～50歳代では0.1％未満，60歳代0.14％，70～80歳代は0.15％を超えている．この傾向は大腸癌の年齢調整死亡率でもみられ，50～60歳代を境に若年者では死亡率は減少傾向，高齢者では増加傾向であることが示されており[5]，年齢に応じた検診方法も今後考慮すべきと思われる．

平成14年度に静岡県大腸がん地域検診で発見された272人の大腸癌のうち155人は早期癌，78人が進行癌であった(39人は記載なしや不明)．また治療は114人がEMRまたはポリペクトミーのみ，115人が外科手術だった(43人は不明など)．検診発見癌は早期癌が多く大腸内視鏡で治療完了するものが約半数を占めていたことになり，早期癌の比率は前述のFDG-PETを併用した宇野らの報告[2]よりも便潜血＋内視鏡精検が高かった．早期癌の治癒率は非常に高いため，大腸癌の早期発見は重要である．この点ではFDG-PETは便潜血＋内視鏡に置き換わるものではないと思われる．言い換えれば，検診としてのFDG-PETの位置付けは便潜血＋大腸内視鏡検査とは別のものとすべきである．

IV. PET検診の問題点

1. コスト

まず高いコストが第一の問題となる．サイクロトロン，薬剤合成装置，PETカメラを装備のうえ，薬剤師やサイクロトロン運転士も必要である．最近では需要増加に伴いFDGのデリバリーも考慮されているようであるが，まだまだ限られた施設の高価な検査である．

2. 被曝と効率

次に被曝と効率性の問題がある．癌発見率が一般の臓器別の検診よりも高く，何より1回の検査でほぼ全身のチェックができることは大変有用であるが，検診では対象は健常者となるため，癌発

見のために全員にFDGで放射線被曝させる必要性があるかは問題である．定期的検診の必要性まで考慮すると被曝量を極力減らす必要がある．またFDG-PET陰性癌も相当数存在するので，ほかの検査との併用も必要となる．

3. 読影，鑑別，他

PETの読影も問題である．唾液腺，咽頭喉頭，心，胃，腸管，腎臓，膀胱には生理的集積がある．この対策として検査前の絶食，注射前後の安静，撮影直前の排尿などが行われている．泌尿器系への生理的集積により骨盤内の癌，とくに膀胱癌は診断率が低いため，最近では水分摂取させて排尿を促す試みもされているようだが，未だ一定の見解はない．また大腸ポリープ，子宮筋腫など良性腫瘍や炎症にも集積するので，癌との鑑別にほかの検査の併用が必要になる．

PET読影の際にはCT，MRIなどとの対比が必要となる．この点でPET-CT検査ではPETとCTが同一画面上で確認できるため診断能力，および労力の面で格段すぐれる．さらに外部線源による吸収補正に要する時間が短くなるため検査時間は30分程度となり，通常PETより約20分短縮される．今後はPET-CTの需要が増えていくと思われる．

医療従事者に対する被曝の問題もある．従来の放射性医薬品よりもエネルギーの高い消滅光子を扱うため，これは大きな問題である．現在は遮蔽励行や自動注入器などで被曝軽減がはかられているが，今後，検査頻度が増すとさらなる対策が必要となる．

おわりに

FDG-PETは形態ではなく機能から得られる画像診断であるため，既存の検査法とは異なる新しいものである．被曝を除くと受診者の身体的負担は非常に少なく全身のスクリーニング検診として期待されるが，未だ有効性に関する科学的評価は出されていない．また一部マスコミ報道にみられるような万能の検査ではなく，かなりの偽陰性が存在するのも事実である．しかしながらこれまでのPET検診で発見される癌のうち大腸癌の占める割合は比較的大きく，費用の問題とPETの特徴を十分理解したうえで，今後，大腸癌検診の一つの選択肢となりうるものと考えている．

文　献

1) 井出　満：FDG-PETを中心とした成人病検診．臨床放射線　49；835-840，2004
2) 宇野公一，呉　勁，鈴木天之，他：FDG-PET検査によるがん検診では何が問題になるのか？臨床放射線　49；841-846，2004
3) 宇野公一：PETによる大腸癌の診断．大腸癌の診断と治療；最新の研究動向．168-172，日本臨牀社，大阪，2003
4) 平成15年度静岡県成人病検診管理指導協議会大腸がん部会資料，2004
5) 吉見逸郎，祖父江友孝：わが国のがん死亡動向．癌と化学療法　31；832-839，2004

Summary

Colorectal cancer screening using PET

Shigeki Yamaguchi*, Hiroyoshi Furukawa**, Hirofumi Morita*, Masayuki Ishii* and Mitsuyoshi Ota*

FDG-PET is a new examination method using glucose and cellular functions. The advantages of PET screening are ; no pain, no preparation, and not specific to any organ. The disadvantages are ; high cost and exposure to radiation. Colorectal cancer was one of the most detectable diseases in Japanese PET screening trials. However, one third of colorectal cancer was PET negative. Also, the early cancer ratio is smaller than that observed using fecal occult blood and colonoscopy. In the Japanese advanced-aged society, PET may have an important role in cancer screening. In the mean time, we need to understand the characteristics of PET.

**Division of Colorectal Surgery, **Divison of Radiology, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi, Shizuoka 411-8777, Japan*

Key words : cancer screening, colorectal cancer, PET

Original Paper

Surgical Outcomes of Laparoscopic *vs.* Open Surgery for Rectal Carcinoma - A Matched Case-control Study

Keisuke Uehara, Seiichiro Yamamoto, Shin Fujita, Takayuki Akasu, Yoshihiro Moriya
Division of Colorectal Surgery, National Cancer Center Hospital in Tokyo, Japan
Corresponding Author: Dr. Seiichiro Yamamoto, Division of Colorectal Surgery
National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan
Tel: +81 3 3542 2511, Fax: +81 3 3542 3815, E-mail: seyamamo@ncc.go.jp

ABSTRACT

Background/Aims: The present study evaluated the short- and middle-term surgical outcomes of laparoscopic surgery (LS) for rectal carcinoma in comparison with a case-control series of open surgery (OS).

Methodology: Between February 1998 and December 2004, 47 patients with rectal carcinoma underwent LS. These patients were compared with a conventional OS group matched for age, gender, location of tumor, surgical procedure, extent of resection and pathological stage.

Results: The median follow-up period for the LS group and the OS group was 25 and 49 months, respectively. In the LS group, median operative time was significantly longer but median blood loss was lower than those in the OS group. There was one requiring conversion to OS. Postoperative intervals until liquid and solid intakes, and hospital stay were significantly shorter in the LS group. Postoperative complications rates are similar and anastomotic leakage occurred in one patient in each group. In the LS group, the levels of white blood cell count on postoperative day 1 and C-reactive protein on postoperative days 1 and 2 were significantly lower than those in the OS group.

Conclusions: LS for rectal carcinoma provides benefits during the early postoperative period without increase in morbidity or mortality.

KEY WORDS: Laparoscopic surgery; Laparoscopic anterior resection; Rectal carcinoma; Case-control study; Surgical outcome

ABBREVIATIONS: Laparoscopic Surgery (LS); Open Surgery (OS); Intersphinctic Rectal Resection and Handsewn Coloanal Anastomosis (ISR-CAA); Abdominoperineal Resection (APR); Randomized Clinical Trial (RCT); White Blood Cell (WBC); C-Reactive Protein (CRP)

INTRODUCTION

Since the first report of laparoscopic colectomy in 1991 by Jacobs *et al.* (1), laparoscopic surgery has been tried and applied to a wide range of colorectal disease, including colorectal carcinoma. Recently many studies have demonstrated several advantages of laparoscopic surgery (LS) over conventional open surgery (OS), including reduced surgical blood loss, decreased postoperative pain and ileus, shorter hospital stay and favorable effects on immunologic status (2-5). With regard to long-term oncological safety, which is the most important concern for LS for malignancies, there have been no reports indicating that LS is inferior to conventional OS by randomized clinical trial (RCT) (6-8).

However, laparoscopic approach to rectal carcinoma is very difficult from a technical standpoint compared for that of colon carcinoma. Following laparoscopic anterior resection for rectal carcinoma, anastomotic leakage has been reported to occur in 7.2-20% (9-15), and as a result, some reports recommended routine covering ileostomy with this procedure even for patients who would not require ileostomy if they selected open anterior resection (9). In fact, many RCTs regarding laparoscopic resection for colorectal carcinoma have excluded patients with middle and lower rectal carcinoma (6-8). Due to the lack of comparative studies, it remains controversial as to whether LS for rectal carcinoma can be regarded minimally invasive surgery.

Since our first laparoscopic surgery for colonic carcinoma in 1993, about 400 patients have undergone laparoscopic resection for colorectal disease at our institution. Because the safety of LS in cancer patients remains to be established, candidates for radical surgery were patients preoperatively diagnosed with T1 or T2 disease. Additionally, LS cases also included patients who were preoperatively diagnosed with T3 but who preferred to undergo LS, as well as those with colon or upper rectal carcinoma for which palliative resection was considered necessary. In June 2001, we unified our surgical and postoperative management procedures, as a consequence, the complication rate and mean length of hospitalization have been reduced at our institution (16,17).

The aim of this study was to analyze the short-term and the middle-term surgical outcomes of LS for patients with rectal carcinoma and compare them with a matched group of patients who underwent similar conventional OS.

METHODOLOGY

Patients

Between February 1998 and December 2004, we

Hepato-Gastroenterology 2006; 53:531-535

TABLE 1 Patient Characteristics

		LS group	OS group	*P* value
No. of patients		47	47	
Sex ratio (male: female)		28: 19	28: 19	>0.999
Age (yr; mean and range)		60 (35-76)	60 (39-84)	0.551
Body mass index (kg/m^2, mean and range)		23.0 (17.3-32.4)	23.2 (18.1-33.8)	0.934
Prior abdominal surgery (%)		13 (27.7)	15 (31.9)	0.823
Location	Upper rectum	25	25	
	Middle rectum	10	10	
	Lower rectum	12	12	
Surgical procedure	Anterior resection	43	43	
	Abdominoperineal resection	1	1	
	Anterior resection with ISR-CAA	3	3	
	Covering ileostomy	11	9	
	Transverse-coloplasty pouch	4	4	
Year of surgery	1997-1999	1	16	
	2000-2002	20	21	
	2003-	26	10	
Pathological stage	UICC Stage 0	2	2	
	UICC Stage I	34	34	
	UICC Stage II	1	1	
	UICC Stage III	10	10	
Follow-up period (month)		24.6 (3.0-65.8)	49.2 (3.7-99.3)	<0.001

ISR-CAA: intersphincteric rectal resection and handsewn coloanal anastomosis.

TABLE 2 Intraoperative and Postoperative Results

	LS group	OS group	*P* valve
Operative time (min.)	255 (117-472)	150 (94-475)	<0.001
Blood loss (mL)	60 (5-477)	72 (10-945)	0.021
Conversion	1	-	-
Liquid intake (days)	1 (1-4)	4 (1-7)	<0.001
Solid intake (days)	3 (2-8)	5 (3-80)	<0.001
Hospital stay (days)	8 (7-23)	15 (10-101)	<0.001

Values are medians (range).

TABLE 3 Morbidities and Mortality

		LS group	OS group	*P* valve
Mortality		0	0	>0.999
Morbidity	Wound sepsis	3	3	>0.999
	Bowel obstruction	1	7	0.059
	Anastomotic leakage	1	1	>0.999
	Anastomotic bleeding	1	0	0.500
	Neurogenic bladder	0	1	0.500
	Pneumonia	1	0	0.500
	Pulmonary embolism	0	1	0.500
Total (No. of patients)		7 (14.9%)	12 (25.5%)	0.304

performed 47 curative laparoscopic resections for patients with rectal carcinoma. All patients were evaluated before surgery by clinical investigation including total colonoscopy, barium enema and computed tomography. To evaluate co-morbid conditions, cardiopulmonary function and renal function test were performed. We excluded the following groups of patients from LS: patients with tumors larger than 7cm, patients with a history of extensive adhesions, patients with intestinal obstruction, and patients with severe obesity (body mass index >32kg/m^2) and patients who did not consent to LS.

The analyzed parameters included age, gender, body mass index, prior abdominal surgery, operative time, blood loss, days until resumption of diet and length of postoperative hospital stay. Pathological staging was performed according to TNM classification. White blood cell (WBC) count and C-reactive protein (CRP) in serum were measured preoperatively and on postoperative day 1 routinely, and on postoperative day 2, if necessary.

Each laparoscopic case was compared with the control OS group of patients matched for age, gender, location of tumor, surgical procedure, extent of resection and pathological stage.

Laparoscopic Technique

Techniques for laparoscopic resection have previously been described (16,17). Initial port placement was performed using the open technique and pneumoperitoneum was induced using carbon dioxide. Two 5-mm ports were then inserted into the left lower mid-abdominal and the left lower quadrant regions, and two other 12-mm ports were inserted into the mid-lower and right mid-abdominal regions under laparoscopic guidance.

The left colon was initially mobilized laterally to medially until the left ureter and superior hypogastric nerve plexus were identified. The mobilization of splenic flexure was performed if necessary. Then, a window was made between the mesocolon containing the arch of the inferior mesenteric vessels and the superior hypogastric nerve plexus, starting at the bifurcation, with support from an assistant holding the sigmoid mesocolon ventrally under traction and to the left using a 5-mm bowel grasper through the left lower quadrant port. After the dissection proceeding to the origin of the inferior mesenteric artery, taking care not to injure the superior hypogastric nerve plexus and the roots of the sympathetic nerves, intracorporeal high ligation of the inferior mesenteric artery was performed. After cutting the inferior mesenteric vein and left colic artery, mobilization of the rectum and mesorectum was performed. The avascular plane between the intact mesorectum anteriorly, and the superior hypogastric nerve plexus, right and left hypogastric nerves, and Waldeyer's fascia posteriorly was entered by sharp dissection, and extended down to the level of the levator muscle for middle and lower rectal carcinomas, taking care to protect the pelvic nerves. For upper rectal lesions, mesorectal tissue extending down to 5cm below the tumor was excised routinely using ultrasonic shears (Laparoscopic Coagulating Shears, Ethicon Endo-Surgery Inc, Cincinnati, OH). Middle and lower rectal tumors were treated by total mesorectal excision. Immediately before rectal transection, laparoscopic rectal clamping was performed just above the anticipated point of rectal transection, using a bowel clamping device intro-

duced through the 12-mm mid-lower port. Rectal washout was performed routinely using 1,000mL of a 5 percent povidone-iodine solution. Rectal transection was then performed by multiple firing technique, using Endo GIA Universal staples, introduced through the 12-mm right mid-abdominal port. A 4- to 5-cm incision was then made over the mid-lower 12-mm port site, and the bowel was exteriorized under wound protection and divided with appropriate proximal clearance. After inserting the anvil head of the circular stapler into the end of the proximal colon, the proximal colon was internalized and the incision was closed. Intracorporeal anastomosis under laparoscopic view was performed by the double-stapling technique (DST) using a circular stapler (ECS 29mm or 33mm, Ethicon Endo-Surgery Inc, Cincinnati, OH). Patients with low anastomosis within 1cm from the dentate line and incomplete "doughnuts" underwent covering ileostomy.

For patients with lesions located within 5cm of the dentate line with more than 2cm of the distal free margin to the dentate line (with no evidence of carcinoma invasion into the sphincters or pelvic floor), laparoscopic intersphincteric rectal resection and handsewn coloanal anastomosis (ISR-CAA) was performed. This surgical technique was described previously (18). For patients undergoing abdominoperineal resection (APR), laparoscopic procedures were followed by perineal dissection in the standard fashion, and end colostomy creation using the left lower abdominal port site.

Statistical Analysis

Statistical analysis was performed using Student's *t* test, the Mann-Whitney *U* test, and the Fisher's exact test as appropriate. A *P* valve of less than 0.05 was considered significant.

RESULTS

Patient demographic characteristics are summarized in **Table 1**. Cases and controls were well matched for gender, age, tumor site, surgical procedure, extent of resection and TNM stage; however, the follow-up period in the OS group was significantly longer than that in the LS group. There were no significant differences in the patient's characteristics, including BMI and rate of prior abdominal surgery, between the two groups. In both groups, three patients underwent ISR-CAA and a transverse-coloplasty pouch was created in 4 patients. Overall, covering ileostomy was required for 11 patients in the LS group, and 9 patients in the OS group. All the patients with covering ileostomy underwent subsequent ileostomy closure.

Surgical and postoperative results are demonstrated in **Table 2**. In the LS group, operative time was significantly longer but blood loss was significantly lower. There was one case requiring conversion to OS because of severe adhesion after repeated cesarean section. Liquid and solid intakes were started on median postoperative days 1 and 3 in the LS group, which

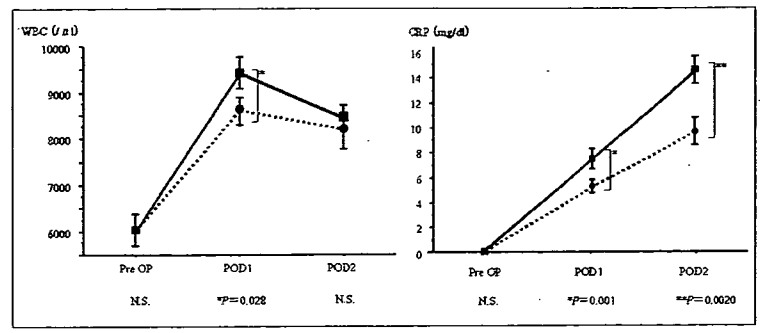


FIGURE 1 The level of white blood cell (WBC) count **(a)** on postoperative day (POD) 1 and the level of serum C-reactive protein (CRP) **(b)** on POD 1and 2 were significantly lower in LS group (●) than OS group (■). Each bar represents the mean standard error.

was significantly shorter than that in the OS group. Similarly, the median postoperative hospital stay was 8 days in the LS group, which was significantly shorter than 15 days in the OS group. All patients were discharged to home.

The postoperative complications are listed in **Table 3**. There were no perioperative mortalities in either group. The rate of postoperative bowel obstruction was 2.1% (1/47) in the LS group and 14.9 % (7/47) in the OS group (P=0.059). An anastomotic leakage occurred in one patient in each group. In the LS group, one patient, who had covering ileostomy during the initial operation, experienced anastomotic leakage that was conservatively managed. In the OS group, a patient with an anastomotic leakage required emergency operation for abdominal drainage and diverting ileostomy. Another patient in the LS group experienced anastomotic bleeding, that was conservatively managed. There was no significant difference in total complication rates between the two groups.

Preoperative and postoperative levels of WBC and CRP in serum are presented in **Figure 1**. In the LS group, the level of WBC on postoperative day 1 and the level of CRP on postoperative day 1 and 2 were significantly lower than those in the OS group.

At the end of the study period, there were no patients who had developed a recurrence or died in this series.

DISCUSSION

To date, there are few studies comparing surgical outcomes between LS *versus* OS for rectal carcinoma (11,19). In this study, we were able to demonstrate that the minimal invasiveness of LS, which has been demonstrated for colon carcinoma, can be preserved in LS for rectal carcinoma as well. Needless to say, the quality of surgery during LS for rectal carcinoma is important. If the rate of conversion to OS increases, outcomes of LS will be shifted to outcomes of OS, thus making it difficult to detect differences between the two groups. In addition, if the complication rate increases, hospitalization after surgery can be prolonged, resulting in a loss of the advantages of LS. In this study, there was only one case requiring conversion to OS, and the anastomotic leakage rate was

lower (2.1%, 1/47) than the rates previously reported. We consider that these facts contributed greatly to demonstrating the minimal invasiveness of LS for rectal carcinoma. And the fact that WBC on postoperative day 1 and CRP values on postoperative day 1 and 2 were significantly lower in the LS group can be regarded as objective data suggesting the minimal invasiveness of LS.

At our institution, there has been much consideration given to the technical safety of LS, and surgeons with a thorough expertise in OS had accumulated enough experience in LS for colon carcinoma, which is technically relatively easy to perform. Thereafter, the indications were expanded to include rectal carcinoma. As a result, LS for rectal carcinoma has been successfully performed with significantly reduced blood loss, earlier start of oral intake and shortened postoperative hospital stay, as compared to OS. At present, the long-term oncological outcome of LS for rectal carcinoma remains unclear and hence the indications for LS for rectal carcinoma remain limited, but it may be technically possible to gradually reduce those limits and expand our indications.

One of the advantages of LS for rectal carcinoma is that by inserting a flexible scope into the narrow pelvis to magnify the operative field, the surgeon can safely mobilize the rectum because of easy identification of the loose connective tissue between the mesorectum and the surrounding tissues such as the hypogastric nerves and the pelvic nerve plexuses, which is not always easy to recognize under direct vision during OS. Another advantage of LS is that everyone participating in the operation can have the same field of view. However, there are several technical limitations in LS. It is often very difficult to occlude and transect the bowel in LS, especially when the tumor is located in the lower rectum. Furthermore, lateral lymph node dissection combined with total mesorectal excision remains the standard surgical procedure for patients with T3 and T4 lower rectal carcinoma in Japan, and lateral lymph node dissection by laparoscopy remain an unexplored frontier (16,20). In particular, previous studies have reported an anastomotic leakage rate of 7.2 to 20% in patients who underwent laparoscopic low anterior resection (9-15), and some authors have recommended covering ileostomy as a routine in this procedure (9). However, this can deteriorate the short-term quality of life of the patient and can also promote local recurrence in the long term (21). Therefore, the utmost effort should be made to avoid this complication.

At our institution, patients with low anastomosis within 1cm from the dentate line, incomplete doughnuts with DST, and laparoscopic intersphincteric rectal resection and handsewn coloanal anastomosis underwent covering ileostomy. However, the decision to perform protective ileostomy in this series was based on much looser criteria than those used in OS in order to avoid major anastomosis complications that could lead to permanent stoma or fatal outcome, especially in the early LS cases involving lower rectal carcinoma. In the future, it may be appropriate to set the same indications for ileostomy as in OS.

In sphincter-preserving surgery for rectal carcinoma, whether performed by LS or by OS, the procedure for dissection and anastomosis is the phase with the highest technical difficulty. For patients with lesions located more than 2cm of the distal free margin to the dentate line with no evidence of carcinoma invasion into the sphincters or pelvic floor, we usually perform laparoscopic DST anastomosis. However, as we previously indicated, during LS for lower rectal carcinoma, the closer the site of dissection of the rectum is to the anus, the more difficult the rectal dissection technique is, thus increasing the use of endolinear staplers needed to perform the dissection. In such cases, it is important to securely penetrate the first and second crossing points using a circular stapler to prevent anastomotic leakage (17).

One of the distinctive points of the present study is that only one patient underwent laparoscopic APR. Recently, laparoscopic ISR-CAA has been reported for patients with lesions located in the lower rectum with greater than 2cm of distal free margin to the dentate line (18). This technique allows a sufficient distal margin to be obtained under direct vision in order to preserve the sphincter and avoid APR. As a consequence, only one patient underwent laparoscopic APR. Although we considered that laparoscopic ISR-CAA was possible in that case, the patient's choice was laparoscopic APR.

With regard to the oncological outcome which is the most important factor in terms of a carcinoma surgery, recently reported results of three RCTs in patients with colon carcinoma or upper rectal carcinoma indicating that the treatment outcome of LS is equal to or better than that of OS (6-8). However, many RCTs have excluded patients with middle and lower rectal carcinoma because of great technical difficulties, and there has been only case series reporting experiences of a single or multiple institutions (2,9-14). Further investigations based on multicenter RCT are necessary for middle and lower rectal carcinoma cases as well.

In conclusion, the findings of the present study demonstrated that LS for rectal carcinoma could be performed safely compared to OS without increased morbidity or mortality. The radical resection of middle and lower rectal carcinoma is a procedure that requires advanced technical skills in OS, to say nothing of LS. With improvements in technology and surgical experience, the indications for this procedure are expected to expand. However, at present, as the oncological outcome remains unclear, expansion of the indications to include advanced lower rectal carcinoma should proceed cautiously.

REFERENCES

1 **Jacobs M, Verdeja JC, Goldstein HS:** Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc

Endosc 1991; 1:144-150.
2 **Breukink SO, Grond AJK, Pierie JP, Hoff C, Wiggers T, Meijerink WJ:** Laparoscopic vs open total mesorectal excision for rectal cancer: an evaluation of the mesorectum's macroscopic quality. Surg Endosc 2005; 19:307-310.
3 **Kiran RP, Delaney CP, Senagore AJ, Milward BL, Fazio VW:** Operative blood loss and use of blood products after laparoscopic and conventional open colorectal operations. Arch Surg 2004; 139:39-42.
4 **Tsang WW, Chung CC, Kwok SY, Li MK:** Minimally invasive surgery for rectal cancer. Surg Clin North Am 2005; 85:61-73.
5 **Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G; Clinical Outcomes of Surgical Therapy (COST) Study Group:** Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA 2002; 287:321-328.
6 **Clinical Outcomes of Surgical Therapy Study Group:** A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004; 350: 2050-2059.
7 **Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J:** Laparoscopic-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomized trial. Lancet 2002; 359:2224-2229.
8 **Leung KL, Kwok SPY, Lam SCW, Lee JF, Yiu RY, Ng SS, Lai PB, Lau WY:** Laparoscopic resection of rectosigmoid carcinoma: prospective randomized trial. Lancet 2004; 363:1187-1192.
9 **Anthuber M, Fuerst A, Elser F, Berger R, Jauch KW:** Outcome of laparoscopic surgery for rectal cancer in 101 patients. Dis Colon Rectum 2003; 46:1047-1053.
10 **Barlehner E, Benhidjeb T, Anders S, Schicke B:** Laparoscopic resection for rectal cancer. Outcomes in 194 patients and review of the literature. Surg Endosc 2005; 19:757-766.
11 **Breukink SO, Pierie JP, Grond AJ, Hoff C, Wiggers T, Meijerink WJ:** Laparoscopic versus open total mesorectal excision: a case-control study. Int J Colorectal Dis 2005; 20:428-433.
12 **Delgado S, Momblan D, Salvador L, Bravo R, Castells A, Ibarzabal A, Pique JM, Lacy AM:** Laparoscopic-assisted approach in rectal cancer patients: lessons learned from >200 patients. Surg Endosc 2004; 18:1457-1462.
13 **Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter J, Marescaux J:** Laparoscopic total mesorectal excision (TME) for rectal cancer surgery: long-term outcomes. Surg Endosc 2004; 18:281-289.
14 **Yamamoto S, Watanabe M, Hasegawa H, Kitajima M:** Prospective evaluation of laparoscopic surgery for rectosigmoidal and rectal carcinoma. Dis Colon Rectum 2002; 45:1648-1654.
15 **Morino M, Giraudo G:** Laparoscopic total mesorectal excision-the Turin experience. Recent Results Cancer Res 2005; 165:167-179.
16 **Yamamoto S, Fujita S, Akasu T, Moriya Y:** A comparison of the complication rates between laparoscopic colectomy and laparoscopic low anterior resection. Surg Endosc 2004; 18:1447-1451.
17 **Yamamoto S, Fujita S, Akasu T, Moriya Y:** Safety of laparoscopic intracorporeal rectal transection with double-stapling technique anastomosis. Surg Laparosc Endosc Percutan Tech 2005; 15:70-74.
18 **Watanabe M, Teramoto T, Hasegawa H, Kitajima M:** Laparoscopic ultralow anterior resection combined with per anum intersphincteric rectal dissection for lower rectal cancer. Dis Colon Rectum 2000; 43:S94-S97.
19 **Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM;** MRC CLASICC trial group: Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005; 365:1718-1726.
20 **Moriya Y, Sugihara K, Akasu T, Fujita S:** Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. World J Surg 1997; 21:728-732.
21 **Bell SW, Walker KG, Rickard MJ, Sinclair G, Dent OF, Chapuis PH, Bokey EL:** Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. Br J Surg 2003; 90:1261-1266.

Jpn J Clin Oncol 2006;36(4)237–244
doi:10.1093/jjco/hyl014

Adjuvant Chemotherapy with Uracil–Tegafur for Pathological Stage III Rectal Cancer after Mesorectal Excision with Selective Lateral Pelvic Lymphadenectomy: A Multicenter Randomized Controlled Trial*

Takayuki Akasu[1], Yoshihiro Moriya[1], Yasuo Ohashi[3], Shigeaki Yoshida[4], Kuniaki Shirao[2] and Susumu Kodaira[5] for the National Surgical Adjuvant Study of Colorectal Cancer[†]

[1]Colorectal Surgery Division, [2]Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, [3]Department of Biostatistics/Epidemiology and Preventive Health Sciences, University of Tokyo, Tokyo, [4]National Cancer Center Hospital East, Kashiwa, Chiba and [5]Department of Surgery, Teikyo University, Tokyo, Japan

Received December 28, 2005; accepted February 22, 2006; published online May 4, 2006

Background: Although adjuvant radiotherapy was proved to be effective for local control of rectal cancer even after standardized mesorectal excision, the role of adjuvant chemotherapy after such standardized surgery remains to be clarified. We aimed to assess the efficacy of a combination of uracil and tegafur for pathological stage III rectal cancer treated by standardized mesorectal excision with selective lateral pelvic lymphadenectomy.
Methods: We randomly assigned patients with completely resected stage III rectal cancer, who underwent standardized mesorectal excision with selective lateral pelvic lymphadenectomy, to receive either oral uracil–tegafur (400 mg/m^2 tegafur per day) for one year or no treatment. Standardization and quality control of the surgery and pathological techniques were ensured by use of the guidelines of the Japanese Society for Cancer of the Colon and Rectum. The primary endpoint was relapse-free survival. The secondary endpoint was overall survival.
Results: We enrolled and randomized 276 patients. Excluding two ineligible patients, 274 were included in the analysis. Planned interim analysis 2 years after accrual termination revealed significant prolongation of relapse-free survival ($P = 0.001$) and overall survival ($P = 0.005$) in the uracil–tegafur group. The 3-year relapse-free survival and overall survival rates were 78 and 91% in the chemotherapy group and 60 and 81% in the surgery-alone group, respectively. Local recurrence rates were low in both groups. Grade 3 events occurred in 17% of the chemotherapy patients, but no grade 4 or more events occurred.
Conclusion: Adjuvant chemotherapy with uracil–tegafur improves survival of patients with stage III rectal cancer after standardized mesorectal excision with selective lateral pelvic lymphadenectomy.

Key words: adjuvant chemotherapy – uracil–tegafur – rectal cancer – surgery

INTRODUCTION

The quality of surgical procedures has prognostic significance for local control and survival in rectal cancer (1,2). However, the lack of standardization for surgery and limitations of surgical information in previous adjuvant trials is well documented (3). The Dutch Colorectal Cancer Group was the first to adopt standardized mesorectal excision (4,5) in a rectal cancer adjuvant study (6). Mesorectal excision involves complete resection of the mesorectum by precise, sharp dissection under direct visualization (4,5) and is recommended in the Guidelines 2000 for Colon and Rectal Cancer Surgery (5).

The Dutch group clearly showed that preoperative radiotherapy is effective for local control even when standardized mesorectal excision is performed (6). Previous studies evaluating adjuvant radiotherapy, but not using standardized surgery, also showed its advantages in local control and

For reprints and all correspondence: Takayuki Akasu, Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: takasu@ncc.go.jp

*This work was presented at the 40th American Society of Clinical Oncology annual meeting, New Orleans, USA, June 5–8, 2004.
†The investigators and institutions participating in the National Surgical Adjuvant Study of Colorectal Cancer are listed at end of report.

survival (7,8). Therefore adjuvant radiotherapy has been recommended as the standard treatment. However, this approach was challenged by the results of a randomized trial which revealed no additional survival benefit from radiotherapy when chemotherapy was administered (9). Furthermore, radiotherapy entails risks of morbidity and mortality (6,7,10–12).

We started the National Surgical Adjuvant Study of Colorectal Cancer 01 randomized trial at the same time as the Dutch trial started (6). The aim of our trial was to evaluate the efficacy of postoperative adjuvant chemotherapy with a combination of uracil and tegafur (a prodrug of fluorouracil) taken orally after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in stage III rectal cancer. Selective lateral pelvic lymphadenectomy is defined as selective application of extended lateral pelvic lymph node dissection, to resect the iliac and obturator lymph nodes when lateral pelvic lymph node involvement is clinically suspected (5,13–15).

We adopted mesorectal excision with selective lateral pelvic lymphadenectomy alone as the control treatment because it was the standard for stage III rectal cancer in Japan (13–15). We did not choose adjuvant radiotherapy because, in addition to the reasons mentioned above, local recurrence rate after mesorectal excision with selective lateral pelvic lymphadenectomy in Japan had been 7–15% in high-volume centers (14,15). Instead, we used oral uracil–tegafur, which was reported to be effective as adjuvant therapy for lung cancer in recent studies (16), because previous studies suggested efficacy of uracil–tegafur for prolonging disease-free survival in rectal cancer (17,18). Bolus fluorouracil and folinic acid, the present world standard for stage III colon cancer, was not used, because folinic acid was not approved in Japan until 1999. We present the results of the planned interim analysis at a median follow-up of 3 years.

METHODS

Patients and Study Design

Enrollment began in October 1996. Eligible patients had undergone a microscopically verified complete resection of pathological stage III adenocarcinoma of the rectum according to the 1992 Tumour Node Metastasis (TNM) Classification of Malignant Tumours (International Union Against Cancer) (19), by standardized mesorectal excision with selective lateral pelvic lymphadenectomy. Other inclusion criteria were the center of the tumor being located between the levels of the first sacral bone and the anal canal; an age of 20–75 years; the absence of preoperative anticancer treatment, previous cancer and synchronous multiple cancers; an Eastern Cooperative Oncology Group performance status of 0, 1 or 2; a leukocyte count of at least 4000/mm^3; a platelet count of at least 100 000/mm^3; serum aspartate aminotransferase and alanine aminotransferase levels that were no more than twice the upper limit of the normal range; a serum total bilirubin level of at most 1.2 mg/dl; a blood urea nitrogen level of at most 25 mg/dl; a serum creatinine level of at most 1.5 mg/dl; normal electrocardiogram; and an absence of severe postoperative complications uncontrolled by the time of registration.

An open-label study design was used. After written informed consent had been obtained, we randomly assigned the patients to postoperative adjuvant treatment with uracil–tegafur or to surgery alone. Randomization was performed by telephone or fax at the central trial office within 42 days after operation. Patients were allocated by the minimization method with Zelen's adjustment for inter-institutional imbalance. The factors used for balancing were the site of the primary tumor (above versus below the rectovesical fossa or rectouterine fossa), primary tumor stage (pT1 or pT2 versus pT3 or pT4) and N stage (pN1 or pN2 versus pN3). The primary endpoint was relapse-free survival and the secondary endpoint was overall survival. The trial was approved by the institutional review board of each participating center.

TREATMENT

Quality Control for Surgery and Pathology

All of the 28 participating centers are the high-volume centers which treated more than 100 colorectal cancer patients per year and institutional members of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (13). The JSCCR has held a general assembly and sessions intended to improve treatment of colorectal cancer twice every year, and has standardized treatment. The JSCCR has provided guidelines for standardized surgical treatment and pathological evaluation (13). All procedures and pathological evaluations were in accordance with the fifth edition of the guidelines published in 1994 (13).

Mesorectal excision was the baseline procedure for all patients. The definitions of the mesorectum and mesorectal excision were the same as those from the Guidelines 2000 (5,13–15). In addition, extended lateral pelvic lymph node dissection (5,13–15) was performed in cases with clinically suspected lateral lymph node disease, as recommended by the JSCCR guidelines (13–15).

The quality of surgery was monitored by the surgeon's report on the location and clinical stage; extent of the resection of the bowel; mesorectum; and lymph nodes, and the pathologist's documentation of the pathological stage; number of resected and positive lymph nodes in each lymph node group; extent of bowel resection; and anal, oral and radial margin status (13).

Adjuvant Chemotherapy

In the treatment group, uracil–tegafur (UFT®, Taiho Pharmaceutical Co., Tokyo, Japan; 400 mg/m^2 tegafur per day) in the form of 100 mg units (100 mg of tegafur plus

224 mg of uracil) was given orally twice daily for 5 consecutive days every weekday for 1 year, starting 6 weeks postoperatively. The dose was rounded up or down to the nearest 100 mg. All patients but one received 3 units of uracil–tegafur (300 mg of tegafur and 672 mg of uracil) twice daily. The patients were asked at each follow-up visit whether they had taken the units as prescribed.

Adverse events were graded according to the toxicity grading criteria of the Japan Clinical Oncology Group, which consist of the Common Toxicity Criteria of the National Cancer Institute with minor modifications (20). Grades range from 0 (none) to 5 (fatal) (20). If a moderate (grade 2) adverse event occurred, the dose of uracil–tegafur was reduced to 250 mg/m^2 per day of tegafur. Treatment was stopped if, despite dose reduction, there was anything of the following: a grade 2 or higher adverse event, a leukocyte count of <3000/mm^3, an aspartate aminotransferase or alanine aminotransferase level of more than 2.6 times the upper limit of the normal range, a total bilirubin level of more than two times the upper limit of the normal range, moderate or severe anorexia, one or more vomitings per day or four or more bowel movements per day.

Follow-up

All the patients were evaluated every 4 months for the first 2 years after surgery and every 6 months for the next 3 years. The evaluation included a physical examination, a complete blood count, blood chemical tests, serum tumor markers, chest roentgenography, and abdominal ultrasonography or computed tomography. A pelvic computed tomography was performed every 6 months. In addition, patients receiving uracil–tegafur had a physical examination, a complete blood count and blood chemical tests every month during the first year.

Statistical Analysis

The sample size was calculated by the method of Schoenfeld and Richter. The study was designed to detect a hazard ratio for relapse or death of 0.67 in the uracil–tegafur group compared with the control group with 80% power at a two-sided α-level of 0.05. Assuming a 5-year relapse-free survival rate of 50% in the surgery-alone group, a 2-year accrual period and a 5-year follow-up, the targeted sample size was 400. In April 2000, the accrual period was extended to 5 years based on the actual accrual rate.

Interim analysis was planned 2 years after accrual termination. Early termination would be considered at the time of the interim analysis if the one-sided P-value of the log-rank test for the primary endpoint was below 0.005, according to the Lan-DeMets spending function method.

Relapse-free survival was defined as the time from surgery until the appearance of the first recurrence of cancer, or death from any cause, and overall survival was defined as the time from surgery until death from any cause. All comparisons between the treatment groups were made on the intention-to-treat principle. Survival curves were estimated by the Kaplan–Meier method, and differences in survival were evaluated with the log-rank test.

RESULTS

Accrual and Interim Analysis

From October 1996 to April 2001, 276 patients were enrolled and randomly assigned to one of the two treatment groups (Fig. 1). The study group decided to stop recruitment in April 2001, because a rapid, further enrollment could not be expected and evaluation of the treatment would be possible through a meta-analysis including the data obtained from this study and existing data (17,18,21). Planned interim analysis was conducted by the data and safety monitoring committee on 13 December 2003. Sufficient results favoring the treatment arm caused the committee to recommend a prompt disclosure of the results. This report is based on the results presented to the data and safety monitoring committee.

Patient Population

Of the 276 enrolled patients 2 (one in each group) proved to be ineligible so that data from 274 patients (139 in the uracil–tegafur group and 135 in the surgery-alone group) were included in the analysis (Fig. 1). The characteristics of the patients are shown in Table 1 and were well balanced in the two groups.

Quality of Surgery

The quality of the surgical procedures (Table 2) was similar in both groups. All patients underwent at least mesorectal excision. Extended lateral pelvic lymph node dissection was added in 38% of the patients, most of whom had a tumor

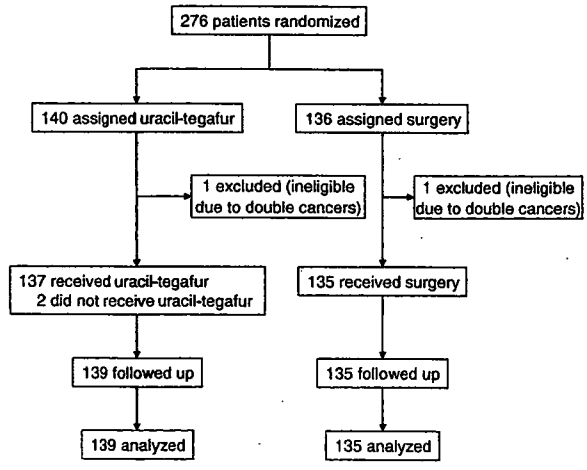


Figure 1. Study profile.

Table 1. Characteristics of the patients

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Age (years, mean [range])	58 (32–75)	57 (30–75)
Sex		
Female	56	53
Male	83	82
Location of the center of the tumor		
Below the promontrium	43	39
Below the lower edge of the second sacral bone	39	43
Below the rectouterine fossa or rectovesical fossa	57	53
Pathological tumor stage*		
T1	8	11
T2	21	16
T3	94	90
T4	16	18
Pathological nodal stage*		
N1	88	89
N2	22	22
N3	29	24
Positive lateral pelvic lymph node	11	7
Type of resection		
Anterior resection	113	109
Hartmann operation	1	0
Abdominoperineal resection	24	25
Other	1	1

*The 1997 TNM Classification of malignant tumors (International Union Against Cancer).

Table 2. Quality of surgery

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Lymph node dissection		
Mesorectal excision	89	81
Mesorectal excision plus extended lateral pelvic lymphadenectomy	50	54
Distal margin of the mesorectum		
2–4 cm	7	2
≥4 cm or total mesorectal excision	132	133
Distal margin of the bowel (cm)		
Median (range)	3 (0.3–10.5)	3.5 (0.5–8)
Number of resected lymph nodes		
Median (range)	21 (1–80)	20 (2–108)

locating below the rectovesical fossa or rectouterine fossa. Distal margins of the mesorectum and rectum were sufficient in both groups. Anal, oral and radial margins were microscopically negative in all the patients. More than 12 lymph nodes were resected in 80% of the patients. The rate of positive lateral pelvic lymph node metastasis was 17% (18/104) in the patients who underwent extended lateral pelvic lymph node dissection.

Table 3. Adverse events

Adverse event	Uracil–tegafur Grade of Toxicity*			Surgery alone Grade of Toxicity*		
	2	3	4	2	3	4
	% of patients					
Leukopenia	5	0	0	1	0	0
Thrombocytopenia	1	0	0	0	0	0
Anemia	4	0	0	2	0	0
Increase in bilirubin	51	9	0	17	2	0
Increase in aspartate aminotransferase	4	2	0	2	0	0
Increase in alanine aminotransferase	10	3	0	6	1	0
Anorexia	7	1	0	1	1	0
Nausea or vomiting	3	1	0	1	1	0
Diarrhea	5	1	0	1	1	1
Skin eruption	6	1	0	0	0	0
Alopecia	0	0	0	0	0	0

*Adverse events were graded according to the toxicity criteria of the Japan Clinical Oncology Group, which consists of the Common Toxicity Criteria of the National Cancer Institute with minor modifications. Grades range from 0 (none) to 5 (fatal).

Adverse Events and Compliance

Of the 139 patients assigned to the uracil–tegafur group, 137 actually took uracil–tegafur and two withdrew from the trial before drug administration (Fig. 1). Moderate (grade 2) and severe (grade 3) events were observed in 65 and 17% of the patients in the uracil–tegafur group and in 39 and 4% of the patients in the surgery-alone group, respectively. Observed adverse events are listed in Table 3. A life-threatening (grade 4) event occurred only in one patient in the surgery-alone group. There was no fatal event.

Compliance with instructions to take uracil–tegafur was calculated on the basis of the number of patients who actually took uracil–tegafur and the number of patients who were assigned to it, excluding those with a recurrence and those who died. The rate of compliance, with or without dose reduction, was 93% at 3 months, 88% at 6 months, 83% at 9 months and 80% at 12 months. The reasons for discontinuation of uracil–tegafur were a cancer recurrence (18 patients), an adverse event (8 patients), patient withdrawal due to adverse events (10 patients) and patient withdrawal due to other causes (4 patients).

Relapse-free Survival

The median follow-up among surviving patients was 3.0 years. At the last follow-up, 32 patients in the uracil–tegafur group

and 53 in the surgery-alone group had recurrence or had died (Table 4). The 3-year estimate of relapse-free survival for the uracil–tegafur group was 78% (95% CI 71–86%). That for the surgery-alone group was 60% (95% CI 51–69%) (Fig. 2). Patients receiving uracil–tegafur had significantly better relapse-free survival than those undergoing surgery alone ($P = 0.0014$). The hazard ratio for any recurrence in the uracil–tegafur group as compared with the surgery-alone group was 0. 52 (95% CI 0. 33–0. 81).

Table 4. Pattern of the first recurrence

	Uracil–tegafur	Surgery alone
Number of patients	139	135
Local alone	6 (4%)	9 (7%)
Anastomotic recurrence	3	4
Pelvic recurrence	3	5
Distant alone	23 (17%)	39 (29%)
Liver metastasis	11	21
Lung metastasis	7	15
Liver and lung metastases	1	0
Others	4	3
Local plus distant recurrences	2	4
Death from other diseases	1	1
Overall events	32 (23%)	53 (39%)

Overall Survival

At the last follow-up, 12 patients in the uracil–tegafur group and 27 in the surgery-alone group had died. The 3-year estimate of overall survival for the uracil–tegafur group was 91% (95% CI 86–97%). That for the surgery-alone group was 81% (95% CI 73–88%) (Fig. 2). Thus patients with uracil–tegafur

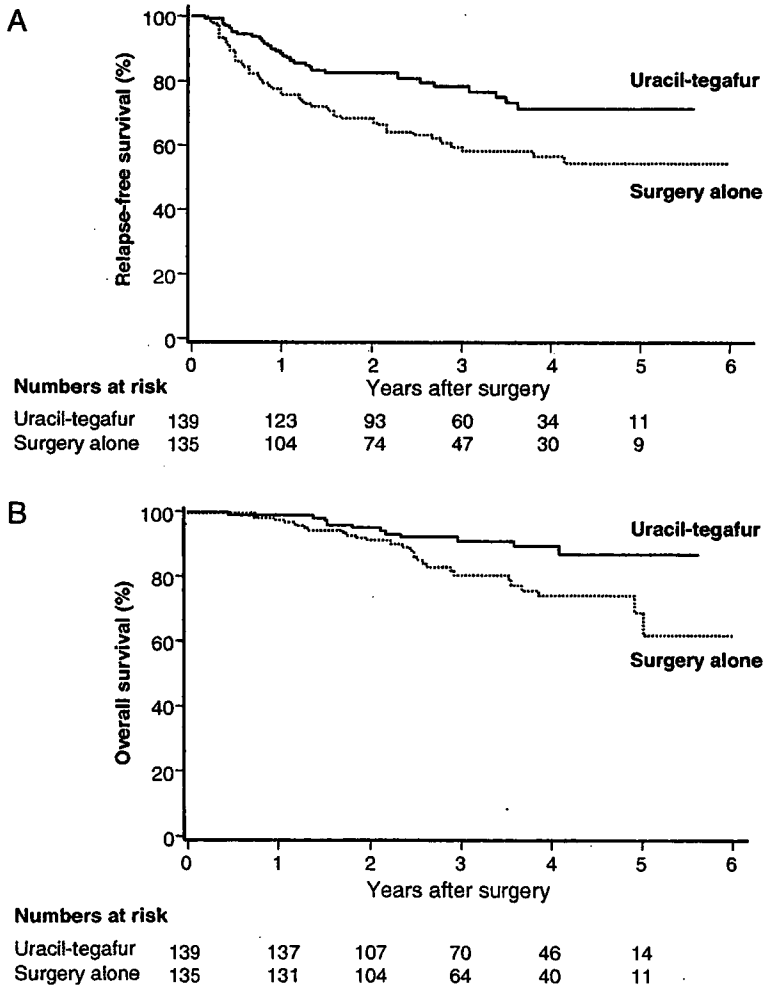


Figure 2. (A) Kaplan–Meier estimates of relapse-free survival. (B) Kaplan–Meier Estimates of overall Survival. At 3 years, the rate of relapse-free survival was 78% in the uracil–tegafur group and 60% in the surgery-alone group ($P = 0.0014$). The rate of overall survival was 91% in the uracil–tegafur group and 81% in the surgery-alone group ($P = 0.0048$).

had significantly better overall survival than those with surgery alone ($P = 0.0048$). The hazard ratio for death in the uracil–tegafur group compared with the control group was 0.42 (95% CI 0. 21–0.83).

Pattern of Recurrence

Details of the pattern of first recurrence are shown in Table 4. At the last follow-up, the rates of overall local recurrence were 5.8% (8/139) for the uracil–tegafur group and 9.6% (13/135) for the surgery-alone group. Adjuvant uracil–tegafur reduced the rates of distant metastases. The rates of overall distant metastases were 18% (25/139) for the uracil–tegafur group and 32% (43/135) for the surgery-alone group. Liver and/or lung metastases composed the majority of distant metastases in both treatment groups.

DISCUSSION

This trial demonstrated the efficacy of postoperative adjuvant chemotherapy with uracil–tegafur after standardized mesorectal excision with selective lateral pelvic lymphadenectomy in pathological stage III rectal cancer. At the planned interim analysis, we found that the 3-year estimate of both relapse-free survival (78%) and overall survival (91%) of the uracil–tegafur group were significantly better than the surgery-alone group (60 and 81%, respectively). The data and safety monitoring committee concluded that the results confirmed the findings of previous studies (17,18) and a recent meta-analysis (21) which showed the effectiveness of uracil–tegafur for rectal cancer.

Rates of local recurrence have been reported to be 20–36% in series of non-standardized, conventional surgery for stage III rectal cancer, with a follow-up of 5 years (3,7,8). For experienced surgeons in mesorectal excision, however, they are 7.5–12% (22,23). At a median follow-up of 3 years, the local recurrence rate was 9.6% in the surgery-alone group of our trial. Although comparisons of such figures should be interpreted cautiously, this shows that a standardized mesorectal excision with selective lateral pelvic lymphadenectomy may achieve good results even in a multicenter setting. Moreover, it may possibly be better than the 2-year local recurrence rate of 8.2% in the mesorectal-excision-alone group of the Dutch trial (6), considering that 56% of patients of the Dutch trial had stage 0–II tumors (6).

Lateral pelvic lymph node metastases from rectal cancer occur outside the mesorectum and appear to account for a major cause of local recurrence. The incidence of lateral pelvic lymph node metastases was reported to be 9–14% (14,15). If the patients have such metastases and undergo only mesorectal excision, the patients have apparent residual tumor in case of recognizable metastases or develop local recurrence after seemingly curative surgery in unrecognizable metastasis cases. Extended lateral pelvic lymph node dissection is a surgical procedure to resect such macroscopic or microscopic metastases (5,14,15). Therefore, this procedure potentially has a similar local-control effect to adjuvant radiotherapy. Whether lateral dissection can be an alternative to radiotherapy should be tested in a randomized controlled trial assessing local control, survival, mortality and morbidity. To conduct such trials, accuracy for detection of lateral pelvic metastases may be a problem. Indeed, in our trial, only 17% of the patients who underwent lateral dissection actually had lateral metastases. To avoid such over-treatment, an accurate diagnostic modality detecting metastasis is necessary.

Between 1990 and 1994, the JSCCR registered 25 224 patients with colorectal cancer. (24) Among them, 2789 patients had curative resection of stage III rectal cancer and their 3-year overall survival rate was 75% (24). In the surgery-alone group of our trial, the 3-year overall survival was 81%. Introduction of revised guidelines, standardized surgical procedures assured by precise documentation and participation of colorectal specialists from high-volume centers may have contributed to this improvement. Quality of surgery is already known as an independent prognostic factor for survival in rectal cancer (1,2), and case volume per surgeon also influences the outcome (3,25).

However, the quality of surgery has no influence on the initial occurrence of distant metastases (1). Even when better-quality surgery reduces local recurrence, occult distant metastases necessitate further treatment to improve survival. We found that, in addition to the efficacy of mesorectal excision with selective lateral pelvic lymphadenectomy, uracil–tegafur further decreased the rate of local recurrence from 9.6 to 5.8%. The rate of distant metastasis was almost halved from 32 to 18%, including a substantial reduction in the rates of liver and lung metastases. Uracil–tegafur appears to improve survival mainly through reduction of distant metastases when applied along with such operations.

The recent meta-analysis assessing randomized controlled trials using oral fluorouracil-based adjuvant chemotherapy for stage I–III colorectal cancer revealed that 1-year chemotherapy reduced the risk of death by 11% ($P = 0.04$) and the risk of recurrence or death by 15% ($P < 0.001$) as compared with surgery alone (21). However, of the three previous randomized trials that compared uracil–tegafur adjuvant therapy with surgery alone in rectal cancer, two revealed significantly improved relapse-free survivals, but none demonstrated an advantage in overall survival (17,18). In these trials, eligible stages were I–III, the dosage of tegafur was 400 mg per day, the compliance was 48–70% and local recurrence rates in surgery-alone group were 19–34% (17,18,21). The significantly better relapse-free and overall survivals in our uracil–tegafur group may be attributable to a selection of stage III patients, a higher dosage of 600 mg per day, better compliance and better quality of surgery. In the meta-analysis, hazard reduction was more marked in early-stage disease (21). In contrast, our results show that a higher dosage may also be effective for advanced-stage disease.

We found that 1-year treatment with uracil–tegafur was safe and well tolerated. Grade 3 events occurred in 16.5% of the patients and consisted mainly of increases in bilirubin

and aminotransferases. No grade 4 or grade 5 events were observed. Previous colon cancer adjuvant trials showed that the overall incidences of grade 3 or more events in patients treated with different regimens were 38% or more for fluorouracil plus folinic acid (26,27), 38% for uracil–tegafur plus folinic acid (27), 30% for capecitabine (26) and more than 41% for oxaliplatin with fluorouracil plus folinic acid (28). The most frequent events included neutropenia, diarrhea, vomiting and hand-foot syndrome. Therefore, the safety profile of uracil–tegafur compares favorably with those of the previous regimens. Consequently, 80% of our patients completed 1 year of treatment, including dose modification. A study using a therapy preference questionnaire demonstrated that, after having experienced both oral and intravenous fluorouracil regimens, most patients preferred an oral regimen (29). The most important reasons for their preference included the convenience of taking the medication at home, less stomatitis and diarrhea, and preference of pills over injections (29). In addition, we should mention that uracil–tegafur is less expensive than the other regimens in this country, where medical costs are becoming an increasingly important issue.

Thus the most significant findings of our trial can be summarized as follows. Peroral monotherapy using uracil–tegafur achieved survival prolongation of stage III rectal cancer patients, without an addition of any other active agents, including folinic acid. This makes it possible to provide less toxic, yet effective, and convenient adjuvant chemotherapy for such patients.

However, several issues may limit the wider applicability of our findings. The numbers of patients recruited were smaller than those of recent rectal cancer adjuvant trials (6,7), although our trial was aimed solely at stage III tumor. The median follow-up time of our study was only 3 years, though disease-free survival with 3-year follow-up is suggested to be an appropriate primary endpoint to replace overall survival with 5-year follow-up (30). We used mesorectal excision with selective lateral pelvic lymphadenectomy that is a standard treatment only in Japan, and did not use mesorectal excision with radiotherapy, a world-standard combination. We could not use fluorouracil plus folinic acid, a standard adjuvant chemotherapy for stage III colon cancer, and neither the recently reported effective regimens including capecitabine and oxaliplatin (26–28). While the standard adjuvant chemotherapy course for colorectal cancer is 6 months (26–28), we opted for chemotherapy of 1 year. Therefore, the appropriateness of our approach should be tested further through comparison with recent standard adjuvant radiotherapy and chemotherapy.

In conclusion, radiotherapy has been considered to be standard adjuvant therapy worldwide for stage III rectal cancer. The present study indicates that uracil–tegafur treatment improves relapse-free survival and overall survival after mesorectal excision with selective lateral pelvic lymphadenectomy. This approach may become one of the treatment options for stage III rectal cancer and may deserve comparison with other treatment approaches.

Acknowledgments

The authors are indebted to Professor J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this manuscript. This study was supported by the Japan Health Sciences Foundation and by Taiho Pharmaceutical Company, Tokyo, Japan.

Members of the National Surgical Adjuvant Study of Colorectal Cancer

Study Chairpersons—S. Yoshida (National Cancer Center Hospital East, Chiba) and S. Kodaira (Teikyo University, Tokyo); Study coordinators—K. Shirao (National Cancer Center Hospital, Tokyo); Y. Shimada (National Cancer enter Hospital, Tokyo); Statistical Analyst—Y. Ohashi (The University of Tokyo, Tokyo); Evaluation Committee—Y. Moriya (National Cancer Center Hospital, Tokyo); S. Imaoka (Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka); T. Kato, (Aichi Cancer Center Hospital, Aichi); S. Kodaira (Teikyo University, Tokyo); E. Ikeda (Yamagata Prefectural Central Hospital, Yamagata); T. Takahashi (Cancer Institute Hospital, Tokyo); Independent Data and Safety Monitoring Committee—N. Saijo (National Cancer Center Hospital East, Chiba); Y. Ariyoshi (Aichi Prefectural Hospital, Aichi); S. Ebihara (National Cancer Center Hospital East, Chiba); H. Origasa (Toyama Medical and Pharmaceutical University, Toyama); M. Fukuoka (Kinki University, Osaka); T. Mitsuishi (Mitsuishi Law & Patent Office, Tokyo); T. Tsuruo (The University of Tokyo, Tokyo); Participating Centers and Investigators—Keiyukai Sapporo Hospital, Hokkaido (M. Hosokawa); Sapporo Kosei General Hospital, Hokkaido (Y. Kondo); National Hospital Organization Sendai Medical Center, Miyagi (T. Saito); Miyagi Cancer Center, Miyagi (Y. Kamiyama, S. Goto); Yamagata Prefectural Central Hospital, Yamagata (E. Ikeda); Ibaraki Prefectural Central Hospital, Ibaraki (F. Yoshimi, Y. Miyata, M. Ohkuwa, H. Ohkura); Tochigi Cancer Center, Tochigi (K. Kotake); Gunma Prefectural Cancer Center, Gunma (S. Sakaue, M. Takahashi); National Cancer Center Hospital East, Chiba (M. Ono, M. Sugito); Cancer Institute Hospital, Tokyo (T. Takahashi, H. Ohta, M. Ueno); National Cancer Center Hospital, Tokyo (Y. Moriya, T. Akasu); International Medical Center of Japan, Tokyo (Y. Saito); Teikyo University Hospital, Tokyo (S. Kodaira, M. Adachi); Tokyo Metropolitan Komagome Hospital, Tokyo (T. Mori, K. Takahashi); Toranomon Hospital, Tokyo (M. Tsurumaru, T. Sawada); Social Insurance Central General Hospital, Tokyo (J. Iwadare); Kanagawa Cancer Center, Kanagawa (S. Takemiya); Niigata Cancer Center Hospital, Niigata (Y. Takii); Aichi Cancer Center Hospital, Aichi (T. Kato); Aichi Prefectural Hospital, Aichi (J. Sakamoto, H. Kojima); Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka (S. Imaoka, M. Kameyama, K. Murata); National Hospital Organization Osaka National Hospital, Osaka (N. Kikkawa, I. Nishisho, H. Mishima); Hyogo

Medical Center for Adults, Hyogo (S. Nakaya, K. Kawaguchi); Okayama Saiseikai General Hospital, Okayama (H. Kimura); Kagawa University Hospital, Kagawa (H. Usuki); National Hospital Organization Shikoku Cancer Center, Ehime (M. Tanada); National Hospital Organization Kyushu Cancer Center, Fukuoka (H. Tomoda, S. Kohnoe, T. Okamura); Kurume University Medical Center, Fukuoka (H. Isomoto).

References

1. Kockerling F, Reymond MA, Altendorf-Hofmann A, Dworak O, Hohenberger W. Influence of surgery on metachronous distant metastases and survival in rectal cancer. *J Clin Oncol* 1998;16:324–9.
2. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedermark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. *Lancet* 2000;356:93–6.
3. Stocchi L, Nelson H, Sargent DJ, O'Connell MJ, Tepper JE, Krook JE, et al. Impact of surgical and pathologic variables in rectal cancer: a United States community and cooperative group report. *J Clin Oncol* 2001;19:3895–902.
4. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; 341: 457–60.
5. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst* 2001;93:583–96.
6. Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638–46.
7. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;336:980–7.
8. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systemic overview of 8507 patients from 22 randomized trials. *Lancet* 2001;358:1291–304.
9. Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 2000;92:388–96.
10. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B, et al. Stockholm Colorectal Cancer Study Group. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer* 2001;92:896–902.
11. Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. *Dis Colon Rectum* 1998;41:543–9.
12. Marijnen CAM, van de Velde CJH, Putter H, van den Brink M, Maas CP, Martijn H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report from a multicenter randomized trial. *J Clin Oncol* 2005;23:1847–58.
13. Japanese Society for Cancer of the Colon and Rectum. General rules for clinical and pathological studies on cancer of the colon, rectum, and anus. 5th ed. Tokyo: Kanehara Shuppan, 1994 (In Japanese).
14. Akasu T, Moriya Y. Abdominopelvic lymphadenectomy with autonomic nerve preservation for carcinoma of the rectum: Japanese experience. In: Wanebo HJ, editor. Surgery for gastrointestinal cancer: a multidisciplinary approach. Philadelphia, PA: Lippincott-Raven, 1997: 667–80.
15. Mori T, Takahashi K, Yasuno M. Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal cancer surgery and its results: the impact of lateral lymph node dissection. *Langenbecks Arch Surg* 1998; 383: 409–15.
16. Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, et al. A randomized trial of adjuvant chemotherapy with uracil–tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004;350:1713–21.
17. Kodaira S, Kikuchi K, Yasutomi M, Takahashi, T, Hojo K, Kato T, et al. Postoperative adjuvant chemotherapy with mitomycin C and UFT for curatively resected rectal cancer: results from the cooperative project No. 7 group of the Japanese Foundation for Multidisciplinary Treatment of Cancer. *Int J Clin Oncol* 1998;3:357–64.
18. Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, et al. Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. *Langenbecks Arch Surg* 2002;386:575–81.
19. Hermanek P, Sobin LH, editors. TNM Classification of Malignant Tumours. 4th edn. New York: Springer-Verlag; 1992.
20. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 1993;23:250–7.
21. Meta-Analysis Group of the Japanese Society for Cancer of the Colon and Rectum and the Meta-Analysis Group in Cancer. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. *J Clin Oncol* 2004;22:484–92.
22. Cecil TD, Sexton R, Moran BJ, Heald RJ. Total mesorectal excision results in low local recurrence rates in lymph node-positive rectal cancer. *Dis Colon Rectum* 2004;47:1145–9.
23. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 1995;181:335–46.
24. Japanese Society for Cancer of the Colon and Rectum. Multi-institutional registry of large bowel cancer in Japan. Vol. 18–22. Utsunomiya: Japanese Society for Cancer of the Colon and Rectum, 1999–2002.
25. Martling A, Cedermark B, Johansson H, Rutqvist LE, Holm T. The surgeon as a prognostic factor after the introduction of total mesorectal excision in the treatment of rectal cancer. *Br J Surg* 2002;89:1008–13.
26. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696–704.
27. Smith RE, Lembersky BC, Wieand HS, Colangelo L, Mamounas EP. UFT/leucovorin vs 5-FU/leucovorin in colon cancer. Oncology 2000;14:24–7.
28. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–51.
29. Borner MM, Schoffski P, de Wit R, Caponigro F, Comella G, Sulkes A, et al. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomized crossover trial in advanced colorectal cancer. Eur J Cancer 2002;38:349–58.
30. Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 2005;23:8664–70.