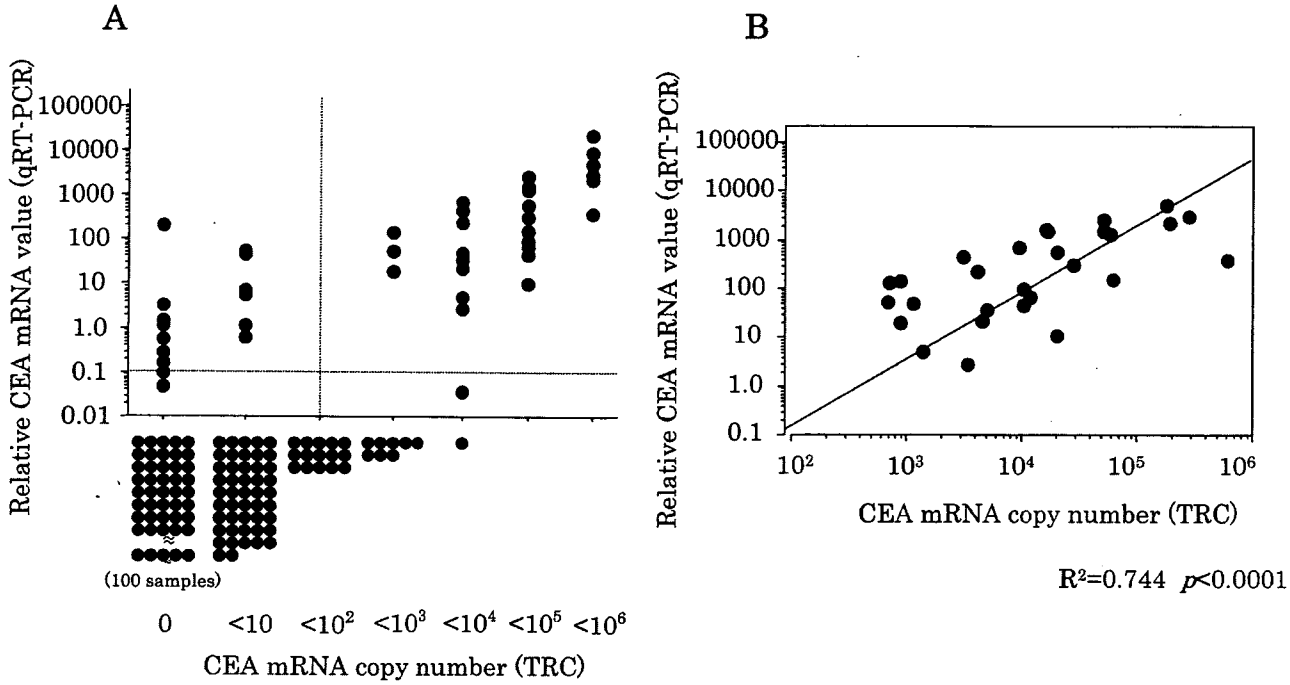

Figure 5. *Concordance between the results of TRC and qRT-PCR for the quantification of CEA mRNA in peritoneal washes from gastric cancer patients. (A) Overall results of the 224 peritoneal washes from 112 gastric cancer patients. Both concordant (right upper area) and discordant cases (left upper and right lower area) are seen. (B) The results from TRC and qRT-PCR double-positive patients. Significant correlation of CEA mRNA values measured by TRC with those of qRT-PCR is observed. Correlation coefficient, $R^2=0.744$ ($p<0.0001$).*

serosa positive cancer (T3) had simultaneous peritoneal metastasis. Another 3 discordant patients who were positive with TRC and negative with RT-PCR were patients with T3 stage cancer, one of whom had simultaneous peritoneal metastasis (Figure 5A and Table III).

Discussion

Sensitive detection of free cancer cells in the peritoneal washes using RT-PCR has now been recognized as a more powerful method for risk assessment of peritoneal recurrence after curative surgery than conventional cytology in gastric cancer (25). However, qRT-PCR still has the following shortcomings: i) cDNA synthesis and subsequent amplification using thermal cycling are so time-consuming that the results are not available during surgery, and ii) the instruments for qRT-PCR are relatively costly, the procedure is somewhat laborious, and therefore still limited to use at general hospitals with research institutions. TRC is one potential modality to overcome these problems. It was first introduced for ultra-rapid genetic diagnosis of occult cancer cells of gastric cancer patients by Ishii *et al.* (20) and offers high detection sensitivity. However, a detailed comparative analysis of TRC and qRT-PCR with a large number of peritoneal wash samples has not previously been meticulously explored. In the present study, we analyzed peritoneal washing

Table III. *Agreement between results of TRC and qRT-PCR method for the detection of CEA mRNA in peritoneal washes from 112 gastric cancer patients.*

	TRC		
	Negative	Positive	
qRT-PCR			
Negative	74	3	
Positive	15	20	
Concordance rate		83.9%	(p<0.0001)

samples collected from 112 patients with early and advanced gastric cancer with both the TRC and qRT-PCR methods. TRC proved to be much faster than qRT-PCR, close to intraoperative conventional cytology. The sensitivity and specificity of the TRC method (85% and 100%, respectively) was superior to cytology (62%, 100%) and was comparable to qRT-PCR (92%, 100%), indicating its availability as an intraoperative sensitive tool for genetic diagnostics in case of peritoneal micrometastasis. However, several points must be discussed and improved in the TRC method.

Determination of the cut-off value of CEA mRNA with TRC is one such issue. We previously determined the optimal cut-off value of CEA mRNA for qRT-PCR using ROC curve

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ORIGINAL ARTICLE

Isolated tumor cell in lateral lymph node has no influences on the prognosis of rectal cancer patients

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Abstract
Background and aims The aim of this study was to determine the incidence of isolated tumor cells (ITC) and micrometastasis in lateral lymph nodes of patients with rectal cancer and its possible correlation with prognosis.
Materials and methods One hundred seventy-seven rectal cancer patients who underwent curative resection with lateral lymph node dissection were enrolled. Dissected lymph nodes were examined using hematoxylin–eosin staining (HE) and immunohistochemistry (IHC) with anti-keratin antibody (AE1/AE3). States of lymph node metastasis were divisible into three groups: detectable with HE (HE+), detectable with only IHC (HE−/IHC+), and undetectable even with IHC (IHC−). Almost all the HE−/IHC+ group was classified as ITC consisting of a few tumor cells according to the UICC criteria (ITC+). Survival rates were compared among HE+, ITC+, and IHC−.
Results ITC+ were detected in 24.1% of patients with HE-negative lateral lymph nodes. No significant difference in overall 5-year survival was observed between ITC+ and IHC− patients (76.1 and 82.9%, respectively, $p=0.25$). Multivariate analysis showed that perirectal HE+ lymph nodes, but not ITC+ lateral lymph nodes, was an independent prognostic factor.
Conclusions ITC in lateral lymph nodes does not contribute to the prognosis of rectal cancer in patients who undergo extended lateral lymph node dissection, unlike HE+ lateral lymph node metastasis.

Keywords Rectal cancer · Lateral lymph node metastasis · Isolated tumor cell · Immunohistochemistry · Lateral lymph node dissection

Introduction

Malignant tumors originating from pelvic urogenital organs such as the uterus and prostate often metastasize to pelvic lymph nodes. The prognostic value and therapeutic significance of pelvic lymph node metastasis in such cancers at certain stages have been determined [1–3]. In rectal cancer, however, pelvic lymph nodes were considered sites of distant metastasis in the studies by Bacon and Sauer [4] and Deddish and Stearns [5] in the 1950s. As a result, total mesorectal excision (TME), in combination with radiotherapy and chemotherapy, had been advocated to improve the therapeutic outcome of rectal cancer [6–11]. In contrast, in Japan, lateral lymph node dissection, which evolved from pelvic node dissection, has developed as an extended requisite procedure for advanced rectal cancer [12–14]. For this reason, pre- or postoperative radiotherapy has not become an established procedure in such cases.

Over the past decade, lymph node micrometastasis from colorectal cancer has been reported as a prognostic factor [15–17], although other studies have claimed the contrary [18–20]. To date, however, only one small-scale study (66 patients) has investigated micrometastasis in lateral lymph

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nodes of patients with rectal cancer in Japan [21]. Recently, the UICC have adopted criteria for micrometastasis as isolated tumor cells (ITC) and "micrometastasis" [22–25], but little is known about the correlation between ITC and the prognosis of colorectal cancer. In this paper, we describe a larger scale immunohistochemical study of lymph node micrometastasis in 177 rectal cancer patients who underwent lateral lymph node dissection, aimed at evaluating the incidence and prognostic value of ITC in lateral lymph nodes.

Materials and methods

Lateral lymph node dissection and surgical procedure

According to the Japanese classification of colorectal carcinoma [25], as shown in Fig. 1, lateral lymph node dissection refers to complete dissection of internal iliac lymph nodes (#272), middle rectal root lymph nodes (#262), and obturator lymph nodes (#282). Lymph nodes such as aortic bifurcation (#280), common iliac (#273), and external iliac lymph (#293) nodes are not necessary, but are usually included in lateral lymph node dissection. Lateral lymph node dissection is performed for curative intent in Japan while those lateral lymph nodes are categorized as distant lymph node in TNM classification. Based on our previous studies of the incidence of lateral lymph node metastases, the pre- or intraoperative indications for lateral lymph node dissection are as follows: the primary cancer located above the peritoneal reflection (upper rectum: Ra) with invasion to the serosa, or non-peritonealized perirectal tissue or deeper, or the primary cancer located below the peritoneal reflection (lower rectum: Rb) or anal canal (P) with invasion to the muscularis propria or deeper. With regard to surgical procedures, mesorectal excision should be performed so that the detached surface is negative for cancer, whereas alignment of the autonomic nerves is confirmed. If infiltration to the nerves is suspected or if lateral lymph node metastasis is macroscopically confirmed, then the ipsilateral autonomic nerves are excised. The upper margin of mesenteric lymph node dissection is the root of the inferior mesenteric artery (#253). The anal margin distance should be 4 cm or more for Ra and 2 cm or more for Rb, and total mesorectal excision is performed for Rb. Lymph nodes located along the bowel axis are classified as lying beneath the tumor (T), on the anal side from the tumor (A), or on the oral side from the tumor (O).

Patient characteristics

Between 1987 and 1999, 581 patients with primary, single rectal cancer underwent initial curative resection at the

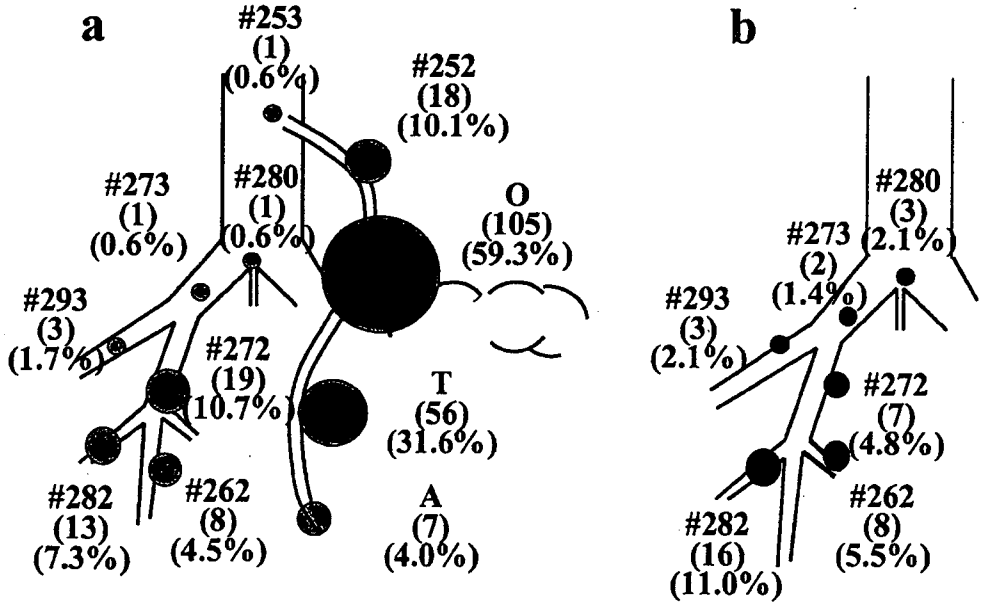

Fig. 1 Numbers of patients with HE+ lateral and perirectal lymph nodes (*LN*) among all 177 patients (a) and those with ITC+ in lateral LN among 145 HE-negative patients (b). Numbers in *upper* and *lower parentheses* mean the number and percentage of node-positive patients, respectively. LNs were classified as common iliac LN (#273), internal iliac LN (#272), middle rectal root LN (#262), obturator LN (#282), aortic bifurcation LN (#280), external iliac LN (#293), inferior mesenteric trunk LN (#252), and inferior mesenteric root LN (#253). LNs along the *bowel axis* were classified as lying beneath the tumor (*T*), on the anal side from the tumor (*A*), and on the oral side from the tumor (*O*)

Department of Gastroenterological Surgery, Aichi Cancer Center Hospital. Of these patients, 177 (112 men and 65 women) underwent lateral lymph node dissection, according to our previously described indication, and were enrolled in this study. No patients have lost to follow-up. Mean patient age was 56.0 years (range, 28–78 years). The histological type was well-differentiated adenocarcinoma in 13 cases, moderately differentiated adenocarcinoma in 145, poorly differentiated adenocarcinoma in 11, and mucinous carcinoma in eight. Rectal cancer mainly affected Ra (n=51), Rb (n=119), and P (n=7; Table 1).

The surgical methods comprised abdominoperineal resection (APR, n=82), low anterior resection (LAR, n=91), and the Hartmann procedure (n=4). The mean number of dissected lymph nodes per patient was 17.0±7.9 for perirectal lymph nodes and 28.4±11.3 for lateral lymph nodes. Follow-up rate was 100%, and median duration of follow-up was 2,472 days (range, 97–5,145 days). Preoperative pelvic irradiation was not performed, and postoperative pelvic irradiation was performed on 23 patients, most of whom had lateral lymph node metastases. Postoperative 5-fluorouracil-based chemotherapy was performed for 70 patients.

Table 1 Characteristics of the 177 rectal cancer patients who underwent curative resection with lateral lymph node dissection

Variables	Values	Percentage
Age (mean years±SD)	56.0±9.9	
Gender		
Male	112	63.3
Female	65	36.7
Tumor location		
Upper rectum (Ra)	51	28.8
Lower rectum (Rb)	119	67.2
Anal canal (P)	7	4.0
pT category		
t2	60	33.9
t3	102	57.6
t4	15	8.5
Stage (TNM)		
1	32	18.1
2	36	20.3
3	109	61.6
Histology		
Well	13	7.3
Moderate	145	81.9
Poor	11	6.2
Mucinous	8	4.5
Perirectal lymph node metastasis		
HE+	79	44.6
HE−	98	55.4
Lateral lymph node metastasis		
HE+	32	18.1
HE−	145	81.9
Harvested lymph node		
Perirectal	17.0±7.9	
Lateral	28.4±11.3	

pT depth of tumor invasion according to UICC
Stage 3 included 32 lateral lymph node metastasis

Immunohistochemical analysis

A total of 5,024 lateral and 3,012 perirectal harvested lymph nodes from 177 patients were examined by routine hematoxylin–eosin (HE) staining, and 32 patients were identified as having lateral HE metastasis (La HE+). Excluding those 32 patients, immunohistochemical analysis was performed on 4,035 lateral lymph nodes of 145 patients without lateral lymph node HE metastasis (La HE−). Micrometastasis was evaluated by two pathologists. Single cancer cells and small cell clusters scattered in sinusoids were regarded as ITC (La ITC+; Fig. 2), and a metastatic focus measuring between 0.2 and 2 mm in diameter was regarded as a "micrometastasis" based on the UICC criteria [22–25]. Contaminating normal epithelial cells and cancer cells from the primary tumors were carefully eliminated to avoid any false-positive results.

For immunohistochemical analysis (IHC), surgically dissected lymph nodes were fixed in buffered formalin, embedded in paraffin, and consecutive 4-μm sections were prepared. IHC was performed using the indirect enzyme-labeled antibody technique with a mouse monoclonal antibody against a broad spectrum of cytokeratin (AE1/AE3, Dako, Copenhagen, Denmark) as the primary antibody as follows. After being deparaffinized with xylene and dehydrated in ethanol, sections were heated in a microwave oven at 98°C for 15 min for antigen retrieval. To inactivate endogenous peroxidase activity, these sections were immersed in methanol with 0.3% hydrogen peroxide for 30 min, followed by normal horse serum for 30 min to block nonspecific reactions. The sections were incubated at 4°C overnight with the AE1/AE3 antibody at 1:100 dilution in phosphate buffered saline (PBS; pH 7.2) containing 1% bovine serum albumin. After washing with PBS, the sections were incubated with a biotinylated second antibody for 30 min. The sections were washed again with PBS, and then incubated with streptavidin–peroxidase complex (Vectastain ABC kit; Vector, Burlingame, CA) for 60 min. The chromogen was developed with 0.01% diaminobenzidine, and the sections were counterstained with Meyer's hematoxylin.

Statistical procedures

Log-rank test using the Kaplan–Meier method was performed, regarding the endpoint as death, including death related to other diseases. For multivariate survival analysis, the Cox hazard model was used. Chi-squared test was used

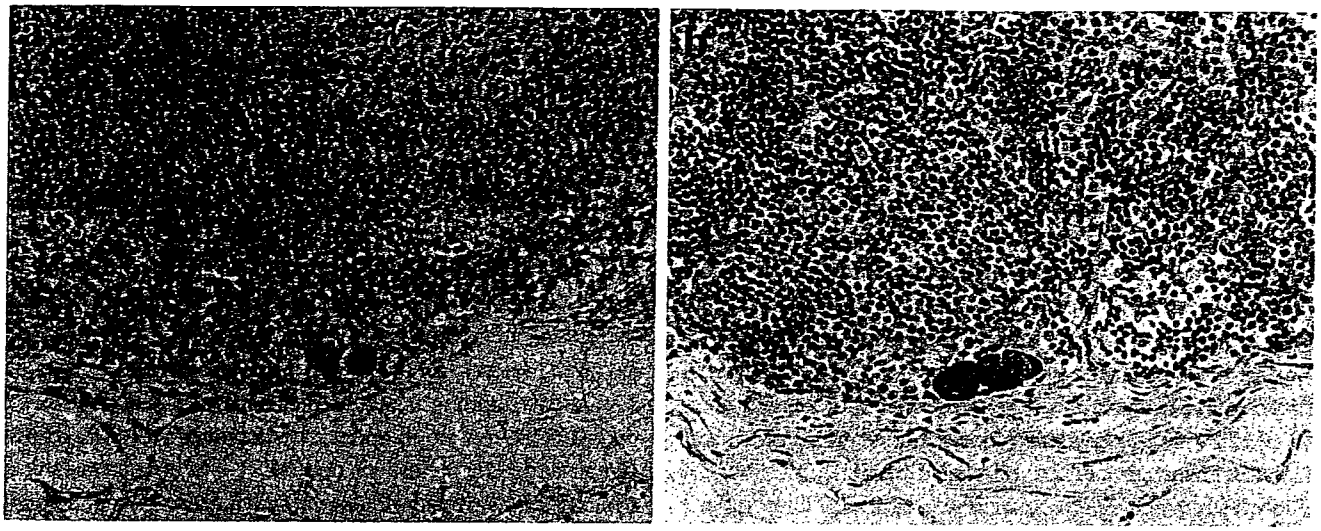

Fig. 2 Micrometastases in lateral lymph nodes stained with anti-cytokeratin antibody. ITC of the single cell type (**a**) and small cluster type (**b**) are seen within the marginal sinus of the lymph node (original magnification, ×200)

to assess differences between groups. The level of significance was set at $p<0.05$.

Results

Incidence of IHC+ lymph nodes

Of 4,035 lateral lymph nodes of 145 La HE− cases, tumor cells were detected in 43 lymph nodes from 36 patients by IHC. Of these 36 patients, one patient (0.7% of La HE−) had one lymph node "micrometastasis" as defined by the UICC, and the remaining 35 patients (24.1% of La HE− cases) were proved to have ITC consisting of the single cell type in 27 patients and the small cluster type in eight patients. The mean number of La ITC+ lymph nodes per patient was 1.2 (range, 1–2; Table 2).

Location of lymph node metastases

The location and incidence of HE+ perirectal and lateral lymph nodes in all 177 patients and of ITC+ lateral lymph nodes in the 145 La HE− patients are represented schematically in Fig. 1a and b, respectively. HE+ and ITC+ lymph nodes were present among middle rectal root lymph nodes in 4.5 and 5.5% of cases, among internal iliac lymph nodes in 10.7 and 4.8% of cases, and among obturator lymph nodes in 7.3 and 11.0% of cases, respectively. The frequency of both La HE+ and La ITC+ was higher around these arteries than in other areas. The total frequency of metastasis (i.e., total of La HE+ and La IHC+) was 2–16% for each area. For lateral lymph nodes, the location and relative frequency of ITC+ lymph nodes were quite similar to those of HE+ lymph nodes.

Table 2 Incidence of micrometastasis in lateral lymph nodes in 177 rectal cancer patients

State of metastasis	No. of patients positive/examined	No. of LN positive/ examined
La HE+	32/177 (18.1%)	59/5024 (1.2%)
La HE−/IHC+		
ITC	35/145 (24.1%)	42/4035 (1.0%)
"micrometastasis"	1/145 (0.69%)	1/4035 (0.02%)
La IHC−	109/177 (61.6%)	3986/4035 (98.8%)

HE+ Metastasis detected by HE staining, *IHC+* metastasis detected by immunohistochemistry, *LN* lymph node

Clinicopathological characteristics of lateral lymph node micrometastasis

The correlation between ITC+ lymph nodes and clinicopathological characteristics was examined (Table 3). The frequency of ITC+ lymph nodes was significantly higher in patients with perirectal HE+ lymph node (32.5%) than in patients without perirectal HE+ lymph node (17.5%, $p=0.03$), and ITC+ patients were significantly more common among women (38.0%) than among men (17.0%, $p=0.005$). No significant differences were observed in other variables.

Survival

During more than 5 years of postoperative follow-up, a total of 57 patients died of cancer recurrence ($n=50$) or other causes ($n=7$). The 5-year overall survival rate for the 177 patients was 72.9%. When survival of patients with lateral lymph node metastasis-negative (La IHC−, $n=109$), ITC-positive (La ITC+, $n=35$), and HE metastasis-positive

Table 3 Correlation between ITC of lateral lymph nodes and clinicopathological parameters

Variables	ITC− (n=109)	ITC+ (n=35)	p value
Age			
> or =60	40 (78.4)	11 (21.6)	0.57
<60	69 (74.2)	24 (25.8)	
Gender			
Female	31 (62.0)	19 (38.0)	0.005
Male	78 (83.0)	16 (17.0)	
Tumor size			
> or =5 cm	54 (77.1)	16 (22.9)	0.69
<5 cm	55 (74.3)	19 (25.7)	
Histology			
Poor/mucinous	8 (61.5)	5 (38.5)	0.21
Well/moderately	101 (77.1)	30 (22.9)	
Preoperative serum CEA			
> or =5	34 (68.0)	16 (32.0)	0.11
<5	75 (79.8)	19 (20.2)	
pT category			
t3–t4	65 (71.4)	26 (28.6)	0.12
t2	44 (83.0)	9 (17.0)	
Vessel invasion			
Positive	78 (76.5)	24 (23.5)	0.74
Negative	31 (73.8)	11 (26.2)	
Lymphatic invasion			
Positive	85 (73.9)	30 (26.1)	0.32
Negative	24 (82.8)	5 (17.2)	
Perirectal lymph node			
HE+	52 (67.5)	25 (32.5)	0.03
HE−	47 (82.5)	10 (17.5)	
Adjuvant chemotherapy			
Yes	37 (78.3)	15 (21.7)	0.34
No	72 (71.2)	20 (28.8)	
Postoperative radiation			
Yes	6 (76.3)	3 (23.7)	0.51
No	103 (66.7)	32 (33.3)	

CEA Serum concentration of carcinoembryonic antigen. *ITC−* One patient with "micrometastasis" is excluded in this group.

(La HE+, n=32) was compared using the Kaplan–Meier method, the 5-year overall survival rates were 82.9, 76.1, and 38.0%, respectively. Apparently, survival of patients with La HE+ was significantly worse than the other two groups (p<0.0001). However, the survival rates of patients with La ITC+ and La IHC− were comparable and showed no significant difference (p=0.25; Fig. 3).

Multivariate analysis (Cox hazard model) of the 144 La HE− patients (excluding one patient with lateral lymph node "micrometastasis") was performed to ascertain prognostic factors for survival (Table 4). This result showed that perirectal lymph node HE metastasis status was significant prognostic factors (p=0.001 and risk ratio 2.3), but La ITC+ status was not a significant prognostic factor (p=0.25 and risk ratio 1.2).

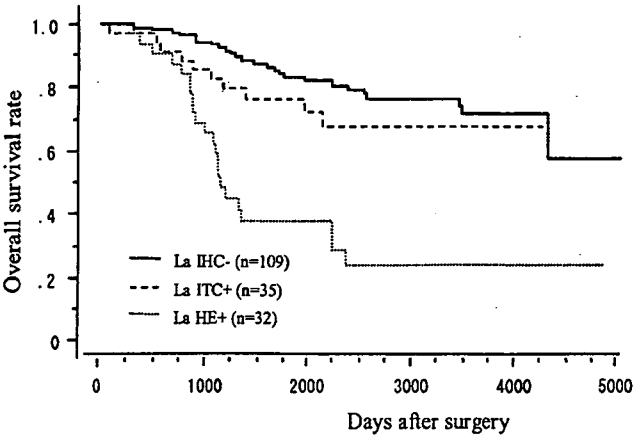

Fig. 3 Survival curves of rectal cancer patients with lateral lymph node dissection stratified according to status of lateral lymph node metastases. Patients with HE+ lateral lymph node is significantly worse than the others (p<0.0001). Survival rate of patients with ITC+ lateral lymph node is not significantly different from those of patients with IHC− lateral lymph nodes (p=0.25)

Discussion

The relationship between lymph node micrometastasis and prognosis in colorectal cancer remains controversial. According to Greenson et al. [15], a difference in the prognosis of Dukes' B colon cancer exists with respect to IHC+ lymph nodes. Several other studies have documented that IHC+ status is correlated with prognosis and local recurrence [16, 17]. However, Isaka et al. [17] found no significant difference in survival rates between IHC+ and IHC− when sufficient numbers of dissected lymph nodes were examined. Later studies also found no significant difference in survival rates when the number of dissected

Table 4 Multivariate analysis (Cox model of regression) of prognostic factors in 144 rectal cancer patients

	Hazard ratio	95%CI	p value
Gender			
Female/male	1.3	0.9–2.0	0.15
Serum CEA			
<5/> or =5	0.8	0.5–1.2	0.32
Histology			
Well, moderate/poor, mucinous	0.6	0.3–1.2	0.16
Depth of tumor invasion (pT)			
t3, t4/t2	1.4	0.9–2.1	0.13
Adjuvant chemotherapy			
Not done/done	1.3	0.8–1.7	0.44
Postoperative radiation			
Not done/done	1.7	0.8–7.5	0.19
Lateral lymph node			
ITC+/IHC−	1.2	0.8–1.9	0.25
Perirectal lymph node			
HE+ / HE−	2.3	1.5–4.1	0.001

lymph nodes was high [26], and at present, no general consensus has been reached on this issue.

On the other hand, the status of micrometastasis in lateral lymph nodes of rectal cancer patients remains largely unknown because of the restricted usage of this radical dissection method in countries other than Japan. Shimoyama et al. [21] previously reported that micrometastasis in lateral lymph nodes is a prognostic factor and that the survival rate of patients with micrometastasis is similar to that of patients with overt nodal metastasis. In the present study, however, we found that ITC+ micrometastasis in lateral lymph nodes of rectal cancer patients had no prognostic significance. There are several possible explanations for this discrepancy between the two studies. One likely reason is the difference in the number of dissected lymph nodes and the number of patients. In Shimoyama's study, the number of dissected lateral lymph nodes was 13.6 per case, whereas in our study, 28.4 and 17.0 nodes per cases were dissected in lateral and perirectal lymph nodes. Tepper et al. [27] and Wong et al. [28] reported a significant difference in survival rates between patients with more than, and less than, 14 dissected lymph nodes, which was comparable to that for patients with HE+ overt lymph node metastasis. The good survival rate we found for patients with numerous dissected lateral lymph nodes is consistent with those previous reports [29, 30]. This suggests that when lymph node dissection is insufficient, which means incomplete histological examination of lymph node, the risk for overlooking HE+ lymph nodes increases. The second possible reason is the classification of micrometastasis. In the present study, almost all the minute metastases in lateral lymph nodes (97%) were identified as ITC by the surgical pathologists. In previous studies, no distinction was made between ITC and "micrometastasis" based on the UICC criteria, suggesting a difference in the extent of micrometastasis between the two studies.

Lateral lymph node metastasis is often regarded as a systemic disease, not a regional one [31, 32]. Indeed, hematogenous recurrent metastasis was common along with local recurrence in La HE+ patients. However, the 5-year survival rate in the present study was approximately 40% for La HE+ patients, as compared with 76.1% for La ITC+ patients and 82.9% for patients with IHC−, indicating relatively good survival of La HE+ patients. Lateral lymph node dissection was originally aimed at improving survival of locally advanced rectal cancer patients by decreasing local recurrence. In fact, the survival efficacy of lateral lymph node dissection due to locoregional control has been demonstrated by retrospective clinical studies in comparison with historical controls [12, 13]. Meanwhile, TME does not take into account lateral lymph node metastasis and would leave residual tumor cells in the pelvic cavity in a considerable number of cases (18.1% for La HE+ and 24.8% for La HE−/IHC+ metastasis). Several trials of TME, in combination with preoperative radiotherapy or adjuvant chemotherapy, proved to eliminate successfully those residual cells and improve locoregional control [9–11]. We therefore consider lateral lymph node dissection as an alternative for preoperative radiotherapy. However, the efficacy of lateral lymph node dissection as a therapeutic option could only be shown by prospective randomized clinical study. Adjuvant postoperative chemotherapy with 5-FU and leucovorin as key drugs for stage III colon cancer [33, 34] has been developing since the 1990s, but in Japan, the survival benefit of adjuvant chemotherapy has not yet been proved for rectal cancer. To evaluate the efficacy of systemic chemotherapy aimed at reducing both hematogenous and local recurrence, further randomized clinical trials of fluorouracil leucovorin–based postoperative adjuvant chemotheraphy with and without lateral lymph node dissection are now ongoing in Japan.

In conclusion, the results of the present study have demonstrated a high incidence of ITC in HE− lateral lymph nodes of rectal cancer patients. However, the survival of patients with ITC+ lateral lymph nodes in whom a sufficient number of perirectal and lateral lymph nodes were dissected was comparable to that of patients with IHC− lymph nodes. These results suggest that ITC in lateral lymph nodes, if excised by sufficient dissection, does not affect the prognosis, unlike the case for HE+ metastases.

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ORIGINAL ARTICLE

Treatment strategy for synchronous metastases of colorectal cancer: is hepatic resection after an observation interval appropriate?

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Abstract
Background In cases of synchronous colorectal hepatic metastases, the primary colorectal cancer strongly influences on the metastases. Our treatment policy has been to conduct hepatic resection for the metastases at an interval of 3 months after colorectal resection. We examined the appropriateness of interval hepatic resection for synchronous hepatic metastasis.
Materials and methods The subjects were 164 patients who underwent resection of hepatic metastasis of colorectal cancer (synchronous, 70 patients; metachronous, 94 patients). Background factors for hepatic metastasis and postoperative results were compared for synchronous and metachronous cases.
Results The cumulative survival rate for 164 patients at 3, 5, and 10 years postoperatively was 71.9%, 51.8%, and 36.6%, and the post-resection recurrence rate in remnant livers was 26.8%. Interval resection for synchronous hepatic metastases was conducted in 49 cases after a mean interval of 131 days. No difference was seen in postoperative outcome between synchronous and metachronous cases.
Conclusion The outcome was similarly favorable in cases of synchronous hepatic metastasis and in cases of metachronous metastasis. Delaying resection allows accurate understanding of the number and location of hepatic metastases, and is beneficial in determining candidates for surgery and in selecting surgical procedure.

Keywords Hepatic metastasis of colorectal cancer · Synchronous hepatic metastasis · Interval hepatic resection

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Introduction

In cases of colorectal cancer with simultaneous hepatic metastasis, the influence of the primary colorectal cancer is stronger than in cases with metachronous metastasis, so the possibility of occult hepatic metastases must be kept in mind. For this reason, the treatment strategies considered in cases of synchronous metastases differ from those in cases of metachronous metastases. Since 1983, the basic policy at our hospital for treating colorectal cancer with synchronous hepatic metastasis has been to resect the primary colorectal cancer, followed, if necessary, by resection of the hepatic metastasis after an observation interval of 3 months. In the present study, we investigated the validity of interval hepatic resection for synchronous hepatic metastases.

Materials and methods

Between January 1983 and December 2003, 223 patients underwent resection at our hospital for colorectal cancer with hepatic metastasis. The subjects for the present study were 164 of these patients who underwent curative resection and had no extrahepatic metastases or recurrences at the time of hepatic resection. The treatment results after hepatic resection in these patients (70 synchronous and 94 metachronous cases) were investigated. A comparison was

made of surgical procedure, number of metastases, presence or absence of macroscopic invasive factors in the vicinity of the metastatic foci (vascular infiltration, bile duct invasion, direct invasion of adjacent viscera, minute satellite, hepatic lymph node metastasis) [1], maximum diameter of hepatic metastatic foci, recurrence in remnant liver, and outcome. Synchronous hepatic metastasis was defined in this study as hepatic metastasis discovered within 6 months after the colorectal operation.

In the statistical analysis, the t test or χ^2 test were used for comparisons between two groups, the Cox proportional hazard model was used for survival analysis, and the logrank test was used for survival rate. A p value of less than 0.05 was considered to indicate a significant difference.

Results

The hepatic resection procedure in the 164 cases was anatomical resection based on hemihepatectomy in 129 cases (78.7%), and partial resection in 35 cases (21.3%). Multivariate analysis was conducted for surgical procedure, metastasis period, number of metastases (single or multiple), presence or absence of invasive factors, and maximum tumor diameter. The results indicated that partial resection, lack of invasive factors, and small tumor diameter were associated with good outcomes. Metastatic period and single or multiple metastases were not significant prognostic factors. A multivariate analysis was conducted for the three factors that were significant in the univariate analysis, and tumor size was shown to be a significant independent prognostic factor (Table 1).

After hepatic resection, recurrence was seen in the remnant liver in 44 cases (26.8%), and the 3-, 5-, and 10-year cumulative survival rates were 71.9, 51.8, and 36.3%, respectively (Fig. 1).

The treatment outcomes in the 70 synchronous cases and 94 metachronous cases were compared. In the 70 synchronous cases, the hepatic resection was conducted simultaneously with the colorectal resection in 21 cases (30.0%) and after an interval in 49 cases (70.0%). The interval from the colorectal surgery until the liver resection was 34–361 days (mean 131 days, median 104 days).

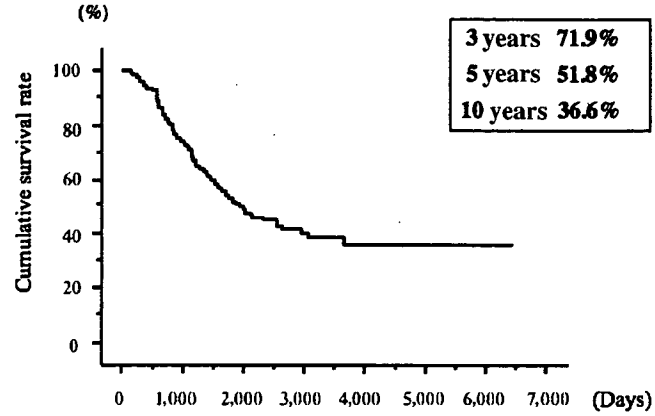

Fig. 1 Postoperative cumulative survival rate in 164 liver metastasis resection patients

No significant difference was found in the maximum diameter of the liver metastases between the two groups, with a mean of 4.5 cm in the synchronous group and 4.9 cm in the metachronous group. The mean number of metastases was greater in the synchronous group (2.2) than in the metachronous group (1.6). Partial resections were conducted in 22 of 70 (31.4%) patients in the synchronous group, which was significantly greater than the 13 of 94 (13.8%) in the metachronous group. Invasive factors were present in 17 (27.9%) synchronous cases and 40 (47.1%) metachronous cases, so a greater proportion of the synchronous cases had no invasive factors (Table 2).

After hepatic resection, recurrence in the remnant liver was seen in 22 of 70 (31.4%) synchronous cases and 22 of 94 (23.4%) metachronous cases. This difference was not significant (p=0.3325). The 3-, 5-, and 10-year postoperative survival rates were 75.0, 55.1, and 34.4% in synchronous cases, and 69.5, 49.1, and 37.3% in metachronous

Table 1 Survival analysis for 164 liver metastasis resections

	Relative risk	95% Lower limit	95% Upper limit	p value
Univariate analysis				
Procedure (anatomical resection/partial resection)	1.845:1.00	1.021	3.336	0.0426
Metastasis period (metachronous/synchronous)	1.077:1.00	0.698	1.663	0.7376
No. metastases (multiple/single)	0.777:1.00	0.502	1.202	0.2576
Invasive factors (no/yes)	0.504:1.00	0.323	0.785	0.0026
Tumor diameter	1.121	1.076	1.171	<0.0001
Multivariate analysis				
Procedure (anatomical resection/partial resection)	1.181:1.00	0.546	2.557	0.6722
Invasive factors (no/yes)	0.686:1.00	0.421	1.120	0.1320
Tumor diameter	1.099	1.045	1.155	0.0002

Table 2 Background factors for synchronous and metachronous metastases

	Synchronous 70 patients	Metachronous 94 patients	*p* value
Tumor diameter (mean) cm	0.3–23 (4.5)	0.9–18 (4.9)	0.4191
No. metastases (mean)	1–10 (2.2)	1–7 (1.6)	0.0133
Procedure (anatomical/partial)	48:22	81:13	0.0115
Invasive factor (yes/no)	17:44	40:45	0.0298

Tumor diameter and number of metastases were tested for significance with the *t* test, and surgical procedure and invasive factor with the chi-square test

cases, respectively. These differences between the groups were also insignificant (Fig. 2).

Discussion

There is much debate as to whether it is better to resect the liver simultaneously with the colon [2–6] or after an interval [7, 8] in cases of colorectal cancer with synchronous hepatic metastases. Few reports, however, mention the length of the interval or changes in hepatic metastatic foci during the interval in such cases of interval hepatic resection [7, 8]. In the present study, we analyzed the outcomes after hepatic resection for metastases of colorectal cancer at our hospital and investigated whether or not the policy of interval hepatic resection for synchronous liver metastases is reasonable.

Since 1983, the main procedure at our hospital for hepatic resection of colorectal cancer metastases has been anatomical resection based on hemihepatectomy and lymph node dissection [1, 9]. Our basic policy has been to wait for an interval of 3 months after resection of the primary lesion and then conduct hepatic resection for the synchronous hepatic metastases. Of the 164 hepatic resection patients in the present study, 129 (78.7%) underwent anatomical resection. In the cases of synchronous liver metastases, 49 of 70 (70.0%) patients underwent hepatic resection after a mean interval of 131 days. In many cases in which synchronous colorectal and hepatic resection was performed, intraoperative palpation revealed a small lesion near the liver surface, and the colorectal surgeon performed a partial resection of the liver, which served as a biopsy.

In the survival analysis of these 164 patients, maximum diameter of hepatic metastasis was an independent prognostic factor [10]. The 3-, 5-, and 10-year cumulative survival rates were 71.9, 51.8, and 36.6%, respectively. There was recurrence in the remnant liver after hepatic resection in 44 (26.8%) patients, and both the postoperative survival rate and recurrence rate in the remnant liver, which indicates local control in the liver, were much better than in reports of other authors [10–14].

It is generally reported that the prognosis is poorer with synchronous hepatic metastases than with metachronous hepatic metastases [15–17]. In our patients, a comparison of background factors in the 70 patients with synchronous metastases and 94 patients with metachronous metastasis revealed no significant differences in tumor diameter, postoperative cumulative survival rate, or recurrence in the remnant liver. In this series of 164 patients, anatomical hepatic resection was performed in 129 (78.7%); among the 70 patients with synchronous metastases, interval hepatic resection was performed in 49 (70.0%). It is unclear how much the choice of procedure [11] and timing for the hepatic resection affected outcome, but among our patients, the

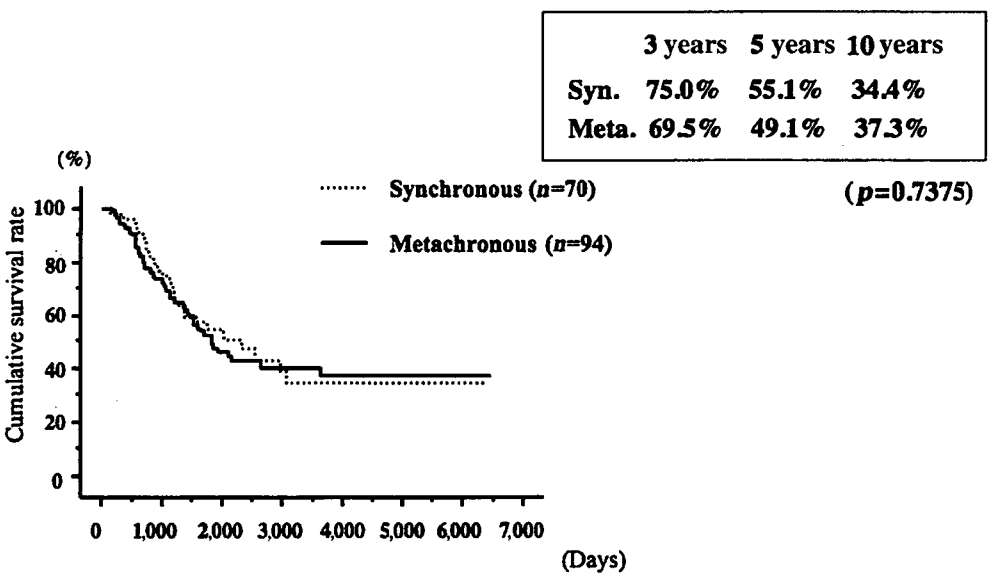

Fig. 2 Postoperative cumulative survival rate with synchronous and metachronous liver metastases

outcome was similarly favorable in cases of synchronous liver metastasis, in which the influence of the primary cancer remains strong, and in cases of metachronous metastasis.

Although there are very few reports on changes in liver metastatic foci during the wait for hepatic resection, or on optimal interval length, Lambert et al. [7] conducted a reevaluation after a mean interval of 6 months in 28 patients with resectable synchronous liver metastases, and reported that there were changes in the surgical indications for liver metastasis in 18 patients (65%) in whom new hepatic lesions or distant metastasis had appeared. Of the patients who underwent colon resection at our hospital between 1995 and 2004, 27 patients had no extrahepatic lesion remnants at the time of colorectal surgery and simultaneously resectable liver metastases. At an interval of 3 months after colorectal resection, there were changes in the planned hepatic resection procedure or surgical indications for liver metastasis in 15 patients (56%). An interval allows the surgeon to gain a more accurate understanding of the number and location of liver metastases from the primary tumor and is beneficial in determining surgical indications or selection of surgical procedure. This treatment policy is thought to contribute to improving the post-hepatectomy outcome and preventing recurrences in the remnant liver in patients with synchronous liver metastases.

From the above, we conclude that interval hepatic resection is a reasonable treatment strategy in cases of synchronous liver metastasis, and that it is beneficial not only in terms of selecting an appropriate procedure for hepatic resection but also in avoiding unnecessary hepatic resections. The liver metastases in our patients grew larger during the interval, and we currently consider an interval of about 3 months to be appropriate, although this will require further investigation in the future.

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An individual patient data meta-analysis of adjuvant therapy with uracil–tegafur (UFT) in patients with curatively resected rectal cancer

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Clinical Studies

An individual patient data meta-analysis of adjuvant therapy with uracil–tegafur (UFT) in patients with curatively resected rectal cancer

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Uracil–Tegafur (UFT), an oral fluorinated pyrimidine chemotherapeutic agent, has been used for adjuvant chemotherapy in curatively resected colorectal cancer patients. Past trials and meta-analyses indicate that it is somewhat effective in extending survival of patients with rectal cancer. The objective of this study was to perform a reappraisal of randomised clinical trials conducted in this field. We designed an individual patient-based meta-analysis of relevant clinical trials to examine the benefit of UFT for curatively resected rectal cancer in terms of overall survival (OS), disease-free survival (DFS), and local relapse-free survival (LRFS). We analysed individual patient data of five adjuvant therapy randomised clinical trials for rectal cancer, which met the predetermined inclusion criteria. These five trials had a combined total of 2091 patients, UFT as adjuvant chemotherapy compared to surgery-alone, 5-year follow-up, intention-to-treat-based analytic strategy, and similar endpoints (OS and DFS). In a pooled analysis, UFT had significant advantage over surgery-alone in terms of both OS (hazard ratio, 0.82; 95% confidence interval (CI), 0.70–0.97; $P = 0.02$) and DFS (hazard ratio, 0.73; 95%CI, 0.63–0.84; $P < 0.0001$). This individual patient-based meta-analysis demonstrated that oral UFT significantly improves both OS and DFS in patients with curatively resected rectal cancer.
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Colorectal cancer accounts for 10–15% of all cancers and is the second leading cause of cancer deaths in developed countries (Pisani *et al*, 1993). In Japan alone, nearly 56 000 new cases are diagnosed and this disease causes 36 000 deaths every year (Statistics and information department, Ministry of Health and Welfare, 1996). Surgical treatment is the primary management of colorectal cancers, with 75–80% of the patients being operable at the time of diagnosis (Boring *et al*, 1991; Vernaba *et al*, 1994). However, even if a curative resection is performed, those patients with regional lymph node involvement (Dukes' C, Stage III) have a 40–50% 5-year survival rate.

Recently, in the field of Stage III colon cancer treatment, adjuvant chemotherapy by 5-fluorouracil (5-FU)/levamisole was proved to be superior to surgery-alone therapy, and then various 5-FU/leucovorin (LV) regimens were confirmed to be effective from the results of numerous large-scale randomised trials and from the pooled analysis of clinical trials (Wolmark *et al*, 1993; International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators, 1995; O'Connell *et al*, 1997). In 2004, results from the Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial demonstrated that combination chemotherapy with 5-FU/LV (de Gramont regimen) plus oxaliplatin was significantly superior to 5-FU/LV alone (André *et al*, 2004). With regard to adjuvant chemotherapy for colon cancer, therefore, solid evidence has been accumulated from relevant clinical trials, and steady evolution of the new treatment modalities has been achieved.

However, the situation is still uncertain focusing on adjuvant therapy for rectal cancer. Despite apparently curative surgery, rectal cancer recurs in more than 55% of the patients, including local recurrence rates of 25% (Vernaba *et al*, 1994). Despite the recommendation of the consensus conference by the National Institute of Health (NIH consensus conference, 1990) that concluded that adjuvant radiotherapy and chemotherapy should be given to all patients with locally advanced rectal cancer, recent findings by a large-scale randomised trial and meta-analysis have failed to prove significant benefit of radiotherapy for survival (Fisher *et al*, 1988; Vernaba *et al*, 1994). In this regard, the quest for an effective adjuvant treatment with a robust advantage on the

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outcome of resected rectal cancer remain an important task for gastrointestinal oncologists.

In Japan, mesorectal excision is standard surgical procedure. Radiotherapy is not routinely performed as adjuvant therapy.

In Japan, adjuvant therapy after resection of colorectal cancer was developed primarily using oral fluorinated pyrimidines (O-FPs). A meta-analysis of three old trials (Sakamoto *et al*, 1999) and a more sophisticated analysis of four recent pivotal randomised trials (Sakamoto *et al*, 2004) demonstrated a statistically significant benefit of O-FPs on the outcome of colorectal cancers over surgery alone. However, the survival benefit shown in that meta-analysis was more pronounced in colon cancers. The risk reduction in terms of rectal cancer was only 8% and the result of those previous meta-analyses that analysed various types of oral fluorinated pyrimidine clinical trials was not sufficient to show a significant effect on survival.

Uracil–tegafur (UFT) is one of the O-FPs. In colon cancer, the majority of recurrences occurred in the liver, whereas in rectal cancer many recurrences occurred in the lung and locally in addition to the liver. Treatment effect may thus differ between colon cancer and rectal cancer. As the previous meta-analysis, two trials of UFT in patients with rectal cancer have been reported. The present study focused on rectal cancer, which lacked a clear-cut survival benefit in our previous meta-analysis. Unlike oral fluoropyrimidines such as carmofur and capecitabine, the formulation of UFT includes a dihydropyrimidine dehydrogenase inhibitor (Diasio, 1999), designed to enhance the bioavailability of FU. This combination of uracil and tegafur was shown, in an animal tumour system, to increase the anti-tumour activity compared with tegafur alone (Ooi *et al*, 2001). UFT also produced an enhanced intratumoural concentration of fluorinated pyrimidine, 5–10 times greater than that achieved with Tegafur alone (Fukunaga *et al*, 1987). Preclinical studies established that the optimal molar ratio of uracil to Tegafur is 4 : 1, which resulted in the highest 5-FU tumour: blood and tumour: normal tissue partition coefficients (Kawaguchi *et al*, 1980). UFT has now been clinically tested for lung cancer (Kato *et al*, 2004), breast cancer (Noguchi *et al*, 2005), and for gastric cancer (Kinoshita *et al*, 2005) in an adjuvant setting in Japan. Recently, UFT has also been tested in Western countries, regarding its efficacy for both advanced and curatively resected colon cancer (Carmichael *et al*, 2002; Douillard *et al*, 2002; Lembersky *et al*, 2006).

Here, we present an individual patient data meta-analysis of five centrally randomised trials recently performed in Japan to compare rectal cancer patients treated with UFT, with the surgery-alone control group. This meta-analysis includes data from more than 2000 patients and therefore provides a more reliable assessment of the effect of UFT on the survival, disease-free survival (DFS), and local relapse-free survival (LRFS) of the patients with rectal cancer than is available from any of the individual studies.

PATIENTS AND METHODS

Selection of trials

Trials that randomly assigned patients to either long-term (12 months) administration of UFT or surgery-alone treatment after curative resection of rectal cancer were eligible for meta-analysis. The randomisation technique used in these trials was the centralised randomisation that precluded the possibility of prior knowledge of the treatment to be allocated.

Five relevant trials identified as Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) 7-1 (Kodaira *et al*, 1998), JFMC15-1, JFMC15-2 (Watanabe *et al*, 2004), Tokai Adjuvant Chemotherapy Study Group for Colorectal Cancer (TAC–CR) (Kato *et al*, 2002), and National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC) (Akasu *et al*, 2006) were included in the meta-analysis involving a total of 2091 patients. In trials JFMC7-1, JFMC15-1, and JFMC 15-2, patients who were randomly assigned to the experimental group received intravenous mitomycin C (6 mg m^{-2}) at 1 week and once monthly for 6 months. In the JFMC15-1 and 15-2 trials, patients who were randomly assigned to the experimental group additionally received an induction course of intravenous 5-FU (250 mg daily^{-1}) during 7 postoperative days (Table 1).

Protocol and data collection for the meta-analysis

In December 2003, a protocol for the meta-analysis, describing the study rationale, statistical methods, and guidelines for publication, was distributed to the principal investigators of the five trials. Investigators were asked to provide individual data for every randomised patient, whether eligible or not, assessable or not, and

Table 1 Details of the randomized controlled trials included in the individual patient data meta-analysis

Category	JFMC7-1	JFMC15-1	JFMC15-2	TAC-CR	NSAS-CC	Total
Additional chemotherapy	Mitomycin C	Mitomycin C+FU IV	Mitomycin C+FU IV	None	None	—
Radiotherapy	None	None	None	None	None	—
UFT dose/day	400 mg	400 mg	400 mg	400 mg	600 mg[a]	—
Period	12 months	12 months	12 months	24 months	12 months	—
Dates of accrual	1986–1988	1989	1990	1991–1994	1996–2001	—
No. of patients	834	447	391	143	276	—
Duration of accrual, months	35	24	24	36	54	—
Sex, No. of patients (male–female ratio)						
Male	521 (62.4%)	260 (58.1%)	244 (62.4%)	93 (65.0%)	167 (60.5%)	1285 (61.4%)
Female	313 (37.6%)	187 (41.9%)	147 (37.6%)	50 (35.0%)	109 (39.5%)	806 (38.9%)
Duke's stage, No. of patients						
A	135	67	62	12	0	276
B	326	175	139	53	0	693
C	373	205	189	78	276	1121
Median age	57	60	59	62	58	58
Upper age limit, years	70	75	75	75	75	—

JFMC = Japanese Foundation for Multidisciplinary Treatment of Cancer; NSAS-CC = National Surgical Adjuvant Study of Colorectal Cancer; TAC–CR = Tokai Adjuvant Chemotherapy for Colorectal Cancer; UFT = Uracil–Tegafur. [a]400 mg m^{-2} day^{-1} for 5 days every 7 days.

properly followed up or not. Items requested for every patient were as follows: patient identification, date of surgery, eligibility, allocated treatment by random assignment, age, sex, primary tumour site, Dukes' stage, induction chemotherapy, dates of recurrence, death, or last visit. Disease-free survival was calculated from the date of surgery to the date of recurrence, second primary cancer or death, whichever occurred first. Survival was calculated from the date of surgery to the date of death, regardless of the cause of death. Local relapse-free survival was calculated from the date of surgery to the date of local recurrence. Data from patients with only distant recurrence and those who were died without recurrence were censored. Patients enrolled in these trials had been followed up for 5–7 years. Toxicity data were not collected, because detailed analysis of side effects can be found in the published reports of the individual trials (Kodaira *et al*, 1998; Kato *et al*, 2002; Watanabe *et al*, 2004; Akasu *et al*, 2006).

All investigators and the Clinical Trial Committee of all the trials agreed to join in the meta-analysis. Individual patient data were received by the independent secretariat by February 2004 and October 2006.

Pretreatment patient characteristics

All 2091 patients had curatively resected rectal cancer without evidence of distant metastasis by diagnostic imaging criteria or by macroscopic examination of the abdominal organs during surgery. Patients with severe postoperative complications were excluded from all trials, as were patients with any previous chemotherapy or radiotherapy or with a synchronous or metachronous second cancer. Median patient age was 61 years at the time of random assignment. The male/female ratio was approximately 3:2. Performance status was less than 2 on the Japan Clinical Oncology Group scale for all patients.

Statistical analysis

The method used for the meta-analysis and the format for the presentation of the results have been described in detail elsewhere (Advanced Colorectal Cancer Meta-Analysis Project, 1992). All analyses were based on individual patient data. Treatment effects on DFS, LRFS, and survival were first estimated within each trial and then combined using classical meta-analytic methods (Colorectal Cancer Collaborative Group, 2001). Treatment effects were displayed as hazard ratios. These ratios were estimated by univariate Cox's proportional model as relative risks of having an event in the UFT group as compared with having the same event in the surgery-alone control group. A ratio less than unity indicates benefit from UFT, and this benefit is statistically significant when the 95% confidence interval (CI) of the ratio does not include unity. The overall effect of treatment was assessed through a χ^2_1 d.f. and the heterogeneity between five trials through a χ^2_4 d.f. (Colorectal Cancer Collaborative Group, 2001). Additional analyses were carried out to determine which of the following prognostic features, if any, were predictive of the treatment effect: Dukes' stage (A *vs* B *vs* C), sex (male *vs* female), and age (three groups of increasing age). Tests for interaction were applied to detect departures from the homogeneity of treatment effects. Multivariate analyses were performed with the use of the Cox proportional hazards regression model for DFS, LRFS, and survival to assess the robustness of the observed effects to adjustments for important covariates and the magnitude of interaction between treatment effect and covariate (Advanced Colorectal Cancer Meta-Analysis Project, 1992). All *P*-values resulted from use of two-sided statistical tests. The significance level was set at 5% for all tests.

RESULTS

Survival

Survival hazard ratios for all the trials are presented in Figure 1. The overall hazard ratio was 0.82 (95% CI, 0.70–0.97; $P=0.02$) with no significant heterogeneity between the treatment effects in different trials (χ^2_4 for heterogeneity $=4.31$; $P=0.37$). UFT showed significant effect on survival of curatively resected rectal cancers with a 5-year survival benefit of approximately 5%.

Figure 2 shows the breakdown of the survival hazard ratio stratified by various patient characteristics. There was a slight trend toward larger treatment benefits in earlier Dukes' stages (Hazard ratio; Dukes' $A=0.60$, Dukes' $B=0.79$, Dukes' $C=0.86$) but heterogeneity tests did not show any significant difference ($\chi^2_2=1.41$; $P=0.495$). There was no statistically significant difference in sex (χ^2_1 for interaction $=1.62$; $P=0.204$) or age (χ^2_2 for interaction $=0.22$; $P=0.898$).

Figure 3 shows survival curves by treatment and disease stage. These curves confirm the hazard ratio analysis shown in Figure 2 and point to favourable effects of UFT in all Dukes' stages.

Disease-free survival

Disease-free survival hazard ratios are presented in Figure 4 for all the trials. These figure show a somewhat larger effect of treatment on DFS than on survival, with an overall DFS ratio of 0.73 (95%CI,

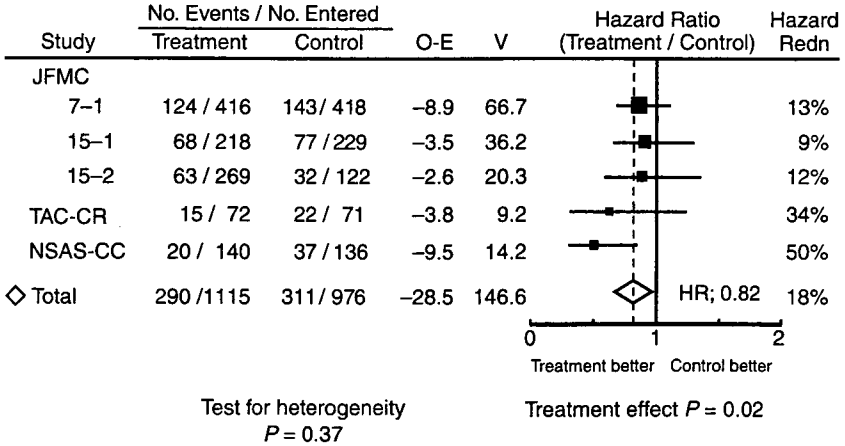


Figure 1 Survival hazard ratios by individual trial (Abbreviations: O/N = observed number of events/number of patients; O–E = Observed minus Expected number of events; V = variance of (O–E); Hazard Redn = hazard reduction; SE = standard error of hazard reduction).

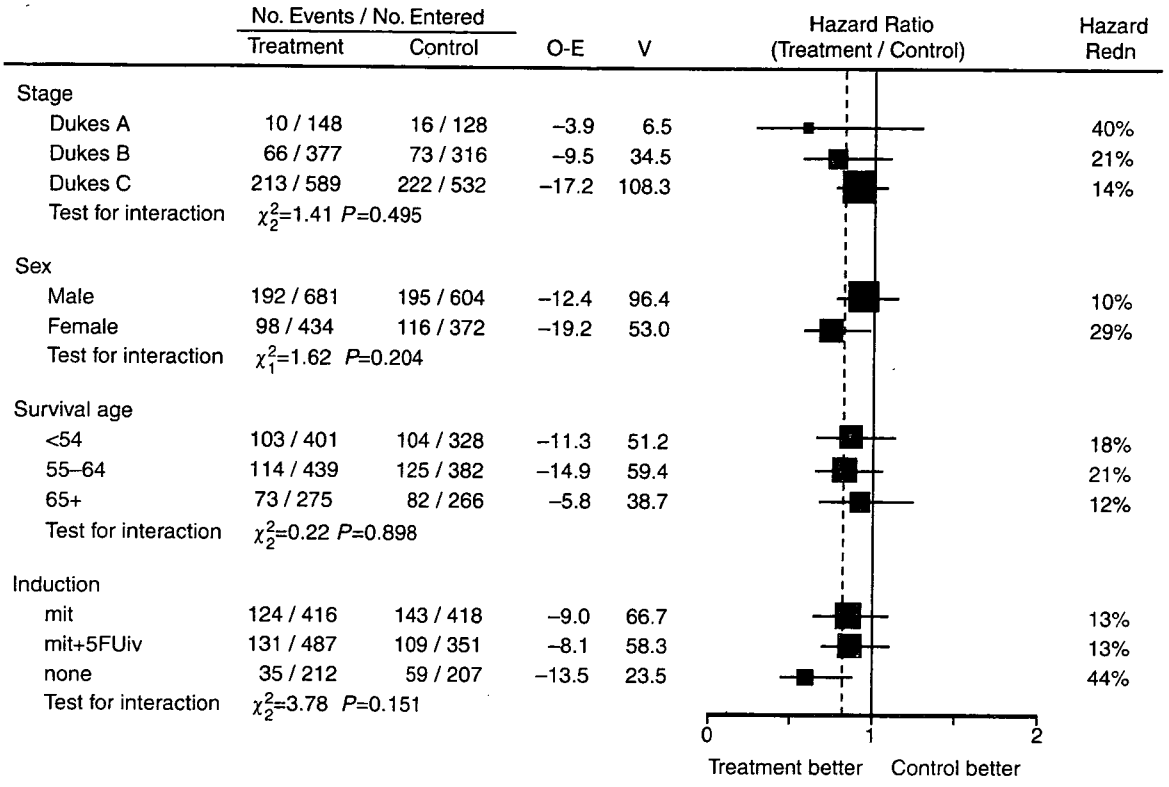
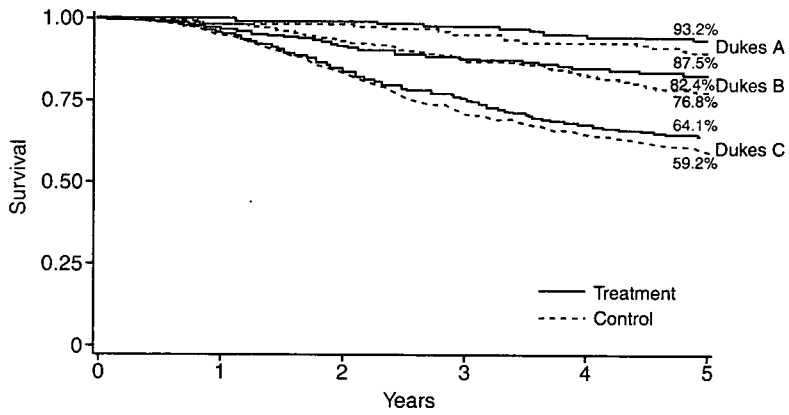


Figure 2 Survival hazard ratios by patient and treatment characteristics (Abbreviations as in Figure 1).



		No. at risk					
Dukes A	Treatment	148	148	147	145	139	137
	Control	128	125	125	121	118	114
Dukes B	Treatment	377	364	343	328	316	304
	Control	316	310	291	273	258	236
Dukes C	Treatment	589	560	494	438	388	357
	Control	532	507	442	374	339	299

Figure 3 Survival curves by tumour stage and by treatment.

0.63–0.84; $P<0.0001$) with a 5-year DFS benefit of 9.7%, but demonstrating some heterogeneity among the treatment effects in different trials (χ^2_4 for heterogeneity = 7.85; $P=0.097$). Additionally, random effect model assuming the variation between trials was applied. The results of the random effect model still revealed highly significant differences owing to the relatively high effect in TAC–CR and NSAS-CC trials.

Figure 5 lists the DFS hazard ratios by various patient and treatment characteristics.

Figure 6 shows DFS curves by treatment and disease stage. These curves again point to benefits of UFT in Dukes' A, B and C stages. Roughly identical effect extended across all Dukes' stages: the DFS benefits at 5 years in terms of risk reduction were 0.42, 0.33, 0.23.

Local relapse free survival

The overall hazard ratio was 0.68 (95%CI, 0.53–0.87; $P=0.0026$), and demonstrating some heterogeneity among the treatment

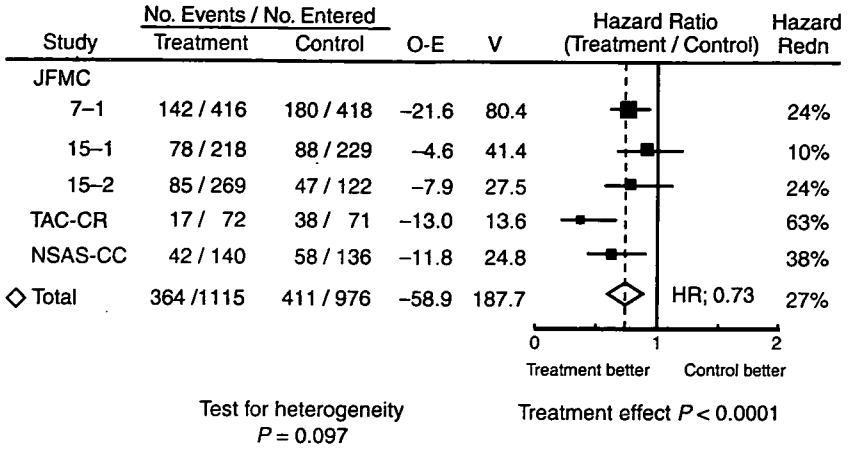


Figure 4 Disease-free survival hazard ratios by individual trial (Abbreviations as in Figure 1).

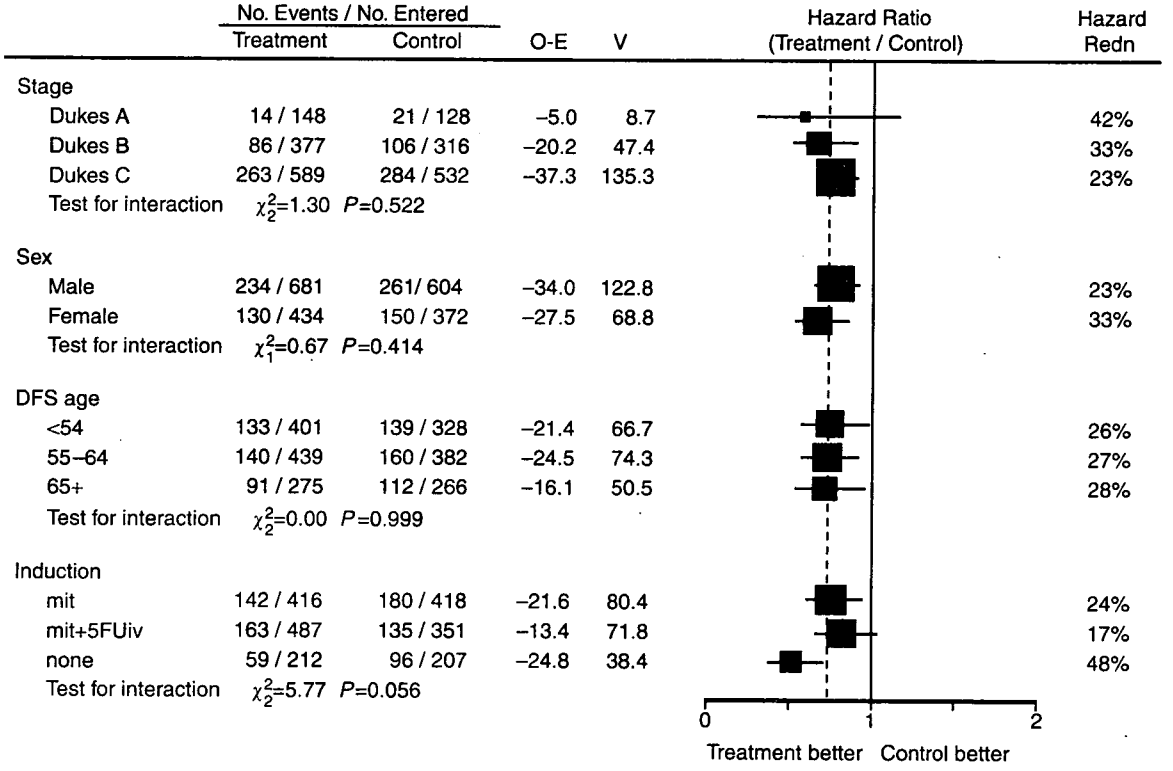


Figure 5 Disease-free survival hazard ratios by patient and treatment characteristics (Abbreviations as in Figure 1).

effects in different trials (χ^2_4 for heterogeneity = 8.82; $P = 0.0658$). UFT also showed significant effect on LRFS of curatively resected rectal cancers.

DISCUSSION

Extensive preclinical and clinical research led to the optimisation of 5-FU administration, with 5-FU bolus in combination with LV as standard therapy both in metastatic disease (Advanced Colorectal Cancer Meta-Analysis Project, 1992) and after curative resection of Stage III (Dukes' C) colon cancer (International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators, 1995; O'Connell *et al*, 1997; Wolmark *et al*, 1999). However, the toxicity of bolus 5-FU/LV regimen, especially the risk of haematologic toxicity and mucositis, could not have been negligible.

Continuous-infusion 5-FU modulated by LV, utilised mostly in European countries, showed somewhat better efficacy and definitely better tolerance than bolus 5-FU in advanced diseases (de Gramont *et al*, 1997; Meta-Analysis Group In Cancer, 1998a, b; Schmoll *et al*, 2000). In the adjuvant setting, one of the continuous regimens (LV5-FU2) was shown to have low toxicity than the bolus regimen, but no difference was shown in terms of survival (André *et al*, 2003). Recently, combination of continuous 5-FU/LV and oxaliplatin (FOLFOX 4) was demonstrated to have significant effect on DFS, and is now considered as the standard adjuvant regimen for colon cancer in the Western world.