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ORIGINAL ARTICLE

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

Yasuhiro Shimizu · Kenzo Yasui · Tsuyoshi Sano · Takashi Hirai · Yukihide Kanemitsu · Koji Komori · Tomoyuki Kato

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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.

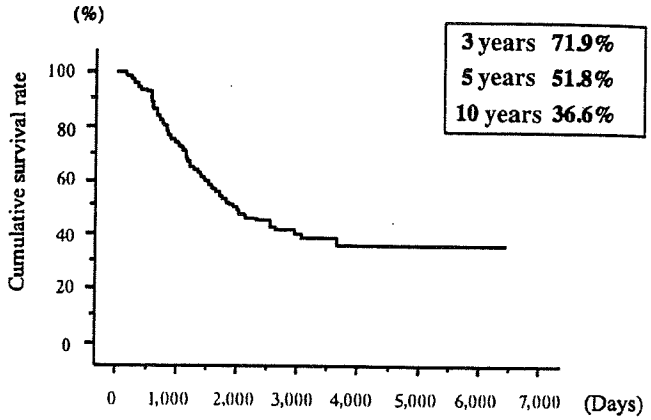

Fig. 1 Postoperative cumulative survival rate in 164 liver metastasis resection patients

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).

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

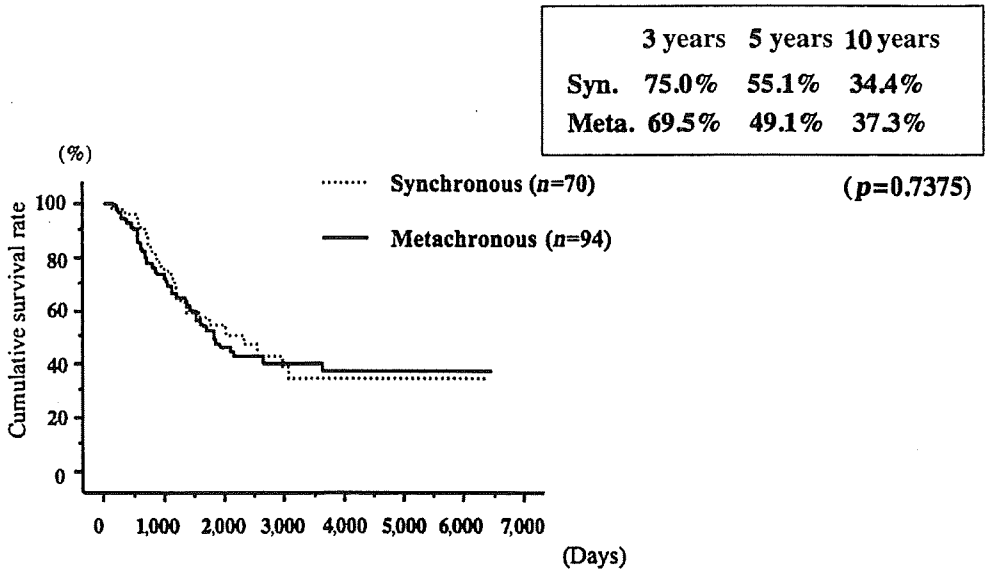

Fig. 2 Postoperative cumulative survival rate with synchronous and metachronous liver metastases

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,

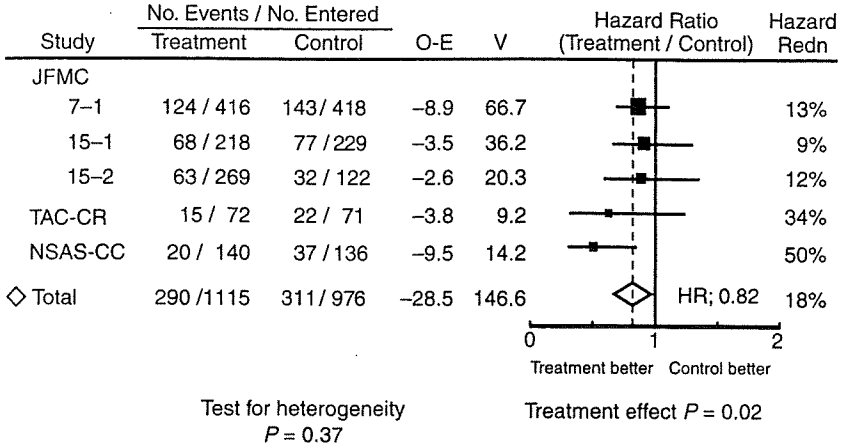


Figure 1 Survival hazard ratios by individual trial (Abbreviations: O/N = observed number of events/number of patients; O−E = Observed minus Expected number of events; V = variance of (O−E); Hazard Redn = hazard reduction; SE = standard error of hazard reduction).

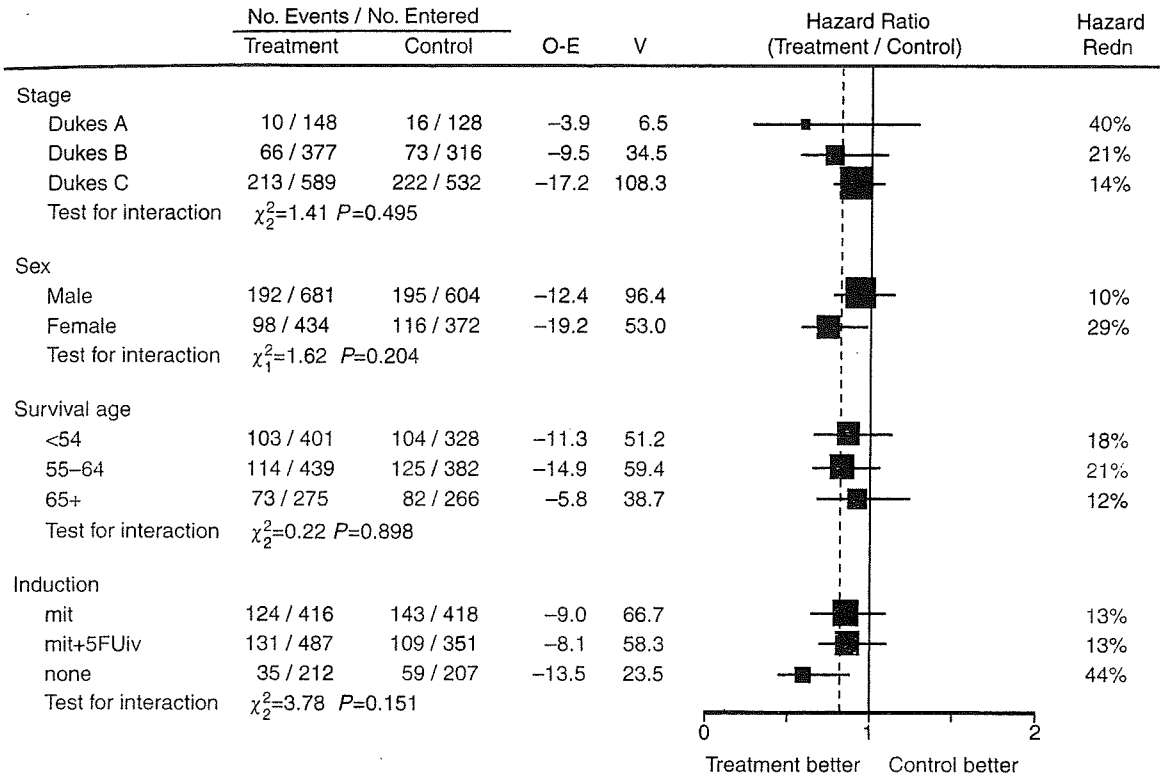
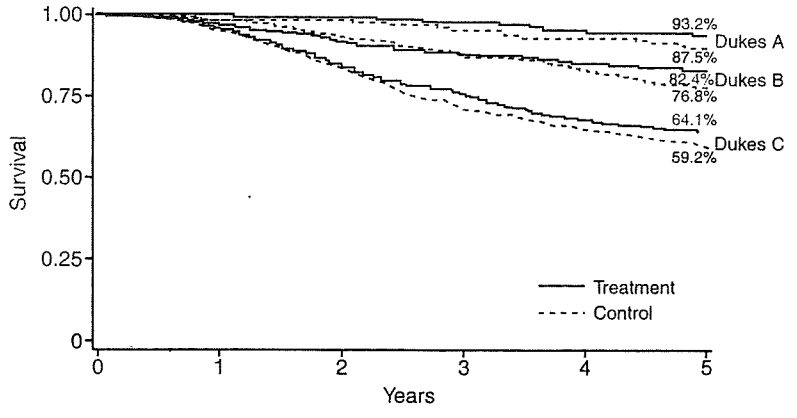


Figure 2 Survival hazard ratios by patient and treatment characteristics (Abbreviations as in Figure 1).



		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

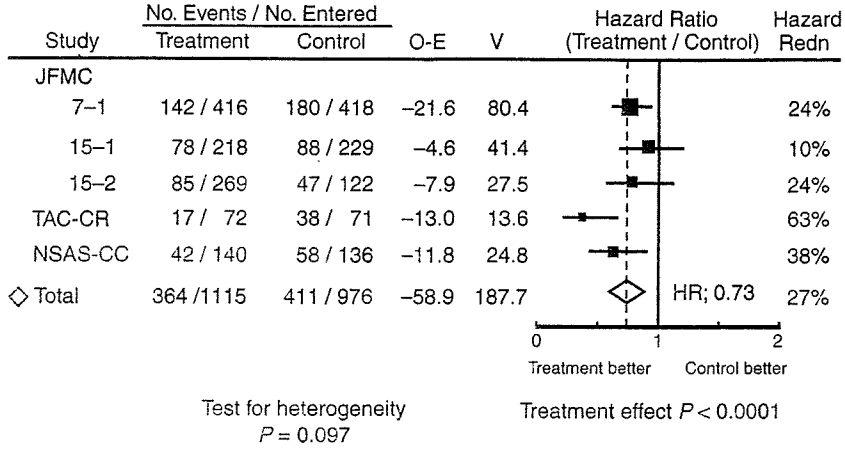


Figure 4 Disease-free survival hazard ratios by individual trial (Abbreviations as in Figure 1).

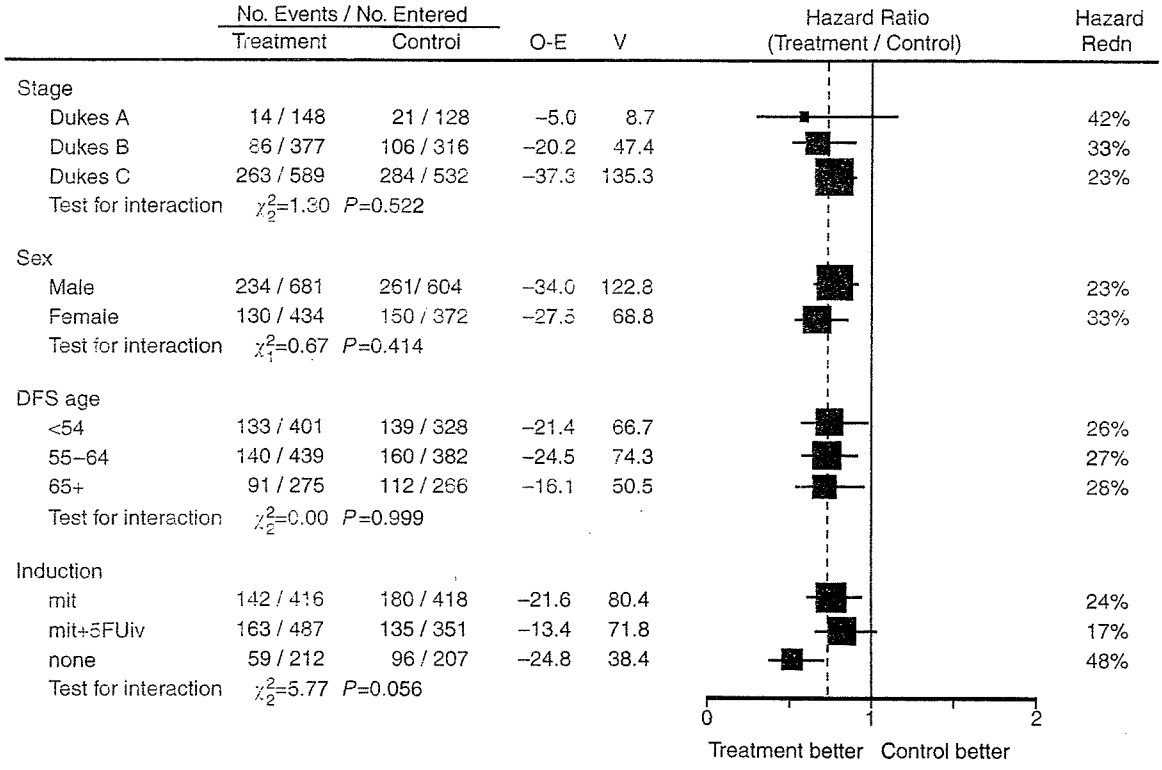


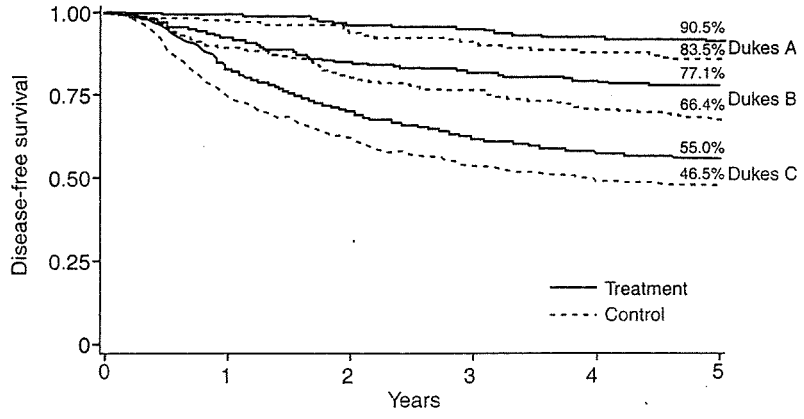
Figure 5 Disease-free survival hazard ratios by patient and treatment characteristics (Abbreviations as in Figure 1).

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.



	No. at risk						
Dukes A	Treatment	148	147	143	140	134	132
	Control	128	124	119	115	111	108
Dukes B	Treatment	377	347	315	303	291	282
	Control	316	280	250	237	217	206
Dukes C	Treatment	589	487	403	354	320	298
	Control	532	396	323	277	251	227

Figure 6 Disease-free survival curves by tumour stage and by treatment.

The recent development of O-FPs has therefore opened new perspectives. Oral fluorinated pyrimidines may mimic continuous regimens without its technical inconvenience and deterring patients' quality of life. In patients with advanced colorectal cancer, the efficacy of UFT (typical and most prescribed O-FP) plus oral LV (Carmichael *et al*, 2002; Douillard *et al*, 2002) or of capecitabine alone (Hoff *et al*, 2001; Van Cutsem *et al*, 2001) seems comparable in terms of the efficacy with significantly less significant severe haematologic toxicities and/or stomatitis. The risk of severe hand-foot syndrome is lower in UFT than with capecitabine, but the risk of severe diarrhoea and other gastrointestinal symptoms is higher in UFT and in UFT/oral LV treatment for Western patients.

In Japan, UFT have been administered for many years especially for patients with curatively resected colorectal cancers. For some unknown reason, severe gastrointestinal toxicities are much less frequent in Japanese patients, and patients usually prefer oral chemotherapy especially in an adjuvant setting (Borner *et al*, 2002).

Furthermore, with regard to rectal cancer, it is a difficult objective for a clinical trial to accrue enough patients, compared to colon cancer, and despite the fact that several attempts of determining a standard adjuvant treatment for rectal cancer, almost no clinical trial has succeeded in showing a relevant survival benefit of adjuvant treatment, except one with preoperative radiotherapy (Swedish Rectal Cancer Trial, 1997).

In this context, several Japanese groups conducted randomised clinical trials comparing UFT with surgery alone for curatively resected rectal cancers. Five such trials were identified after a meticulous search, and are included in the present meta-analysis. This meta-analysis was restricted to trials that had been randomised centrally and from which no patient had been excluded for any reason. It represents the largest series of properly randomly assigned patients receiving the single oral adjuvant O-FP agent, that is, UFT, for rectal cancer comparing with patients receiving no therapy after curative tumour resection.

This meta-analysis found a statistically significant benefit of UFT with regard to overall survival (OS) (hazard ratio = 0.82; $P = 0.02$) as well as DFS (hazard ratio = 0.73; $P < 0.0001$), and LRFS (hazard ratio = 0.68; $P = 0.0026$). As can seen by comparing the data in Figures 1 and 4, the data from the NSAS-CC and TAC-CR study show benefits that are, apparently, larger than the others. As shown in Table 1, the dosage and duration of treatment with UFT in the NSAS-CC and TAC-CR trials differed from those in the other three trials; the dose intensity of UFT was higher in the former two trials. Several studies have reported that a high-dose intensity of UFT improves survival in patients given postoperative adjuvant chemotherapy for gastric cancer (Sugimachi *et al*, 1997; Danno *et al*, 2001). The higher dose intensity of UFT in the NSAS-CC and TAC-CR trials may have influenced the outcomes.

Most of the Japanese rectal cancer patients did not receive pre- or postoperative radiotherapy in any of the trials. Although radiotherapy has been considered one of the standard adjuvant treatments in the Western countries, significant survival benefit has not been shown with reproducibility (Wolmark *et al*, 2000; Colorectal Cancer Collaborative Group, 2001). The ostensible advantage of adjuvant radiotherapy is to decrease local recurrence of rectal cancers. As compared with postoperative chemoradiotherapy, preoperative chemoradiotherapy does not improve OS, but inhibits local recurrence and reduces toxicity (Sauer *et al*, 2004). In our study, however, LRFS was also significantly better in the UFT group compared to surgery alone group. As far as our results are concerned, UFT might also be useful in preventing local recurrence in Japanese patients who usually do not receive radiotherapy in an adjuvant setting.

Also, there is still a debate whether adjuvant chemotherapy for early stage rectal cancer is feasible (Buyse and Piedbois, 2001). In terms of numbers needed to treat, these benefits imply that approximately 20 patients need to be treated for one more patient to survive 5 years, and approximately 10 to be treated for one fewer patient to suffer a cancer recurrence within 5 years, regardless of disease stage. Our results show that the therapy is beneficial in Stage II patients not only Stage III patients with nodal involvement (Mamounas *et al*, 1999; Gray *et al*, 2004). As for early stage disease, further investigations are needed to assess potential benefits of treatment because events were infrequent and hazard ratios were small.

Regardless of the disease stage and patient background characteristics, there is a need for further trials involving UFT and new agents that are effective in advanced disease, such as irinotecan, oxaliplatin, and monoclonal antibodies.

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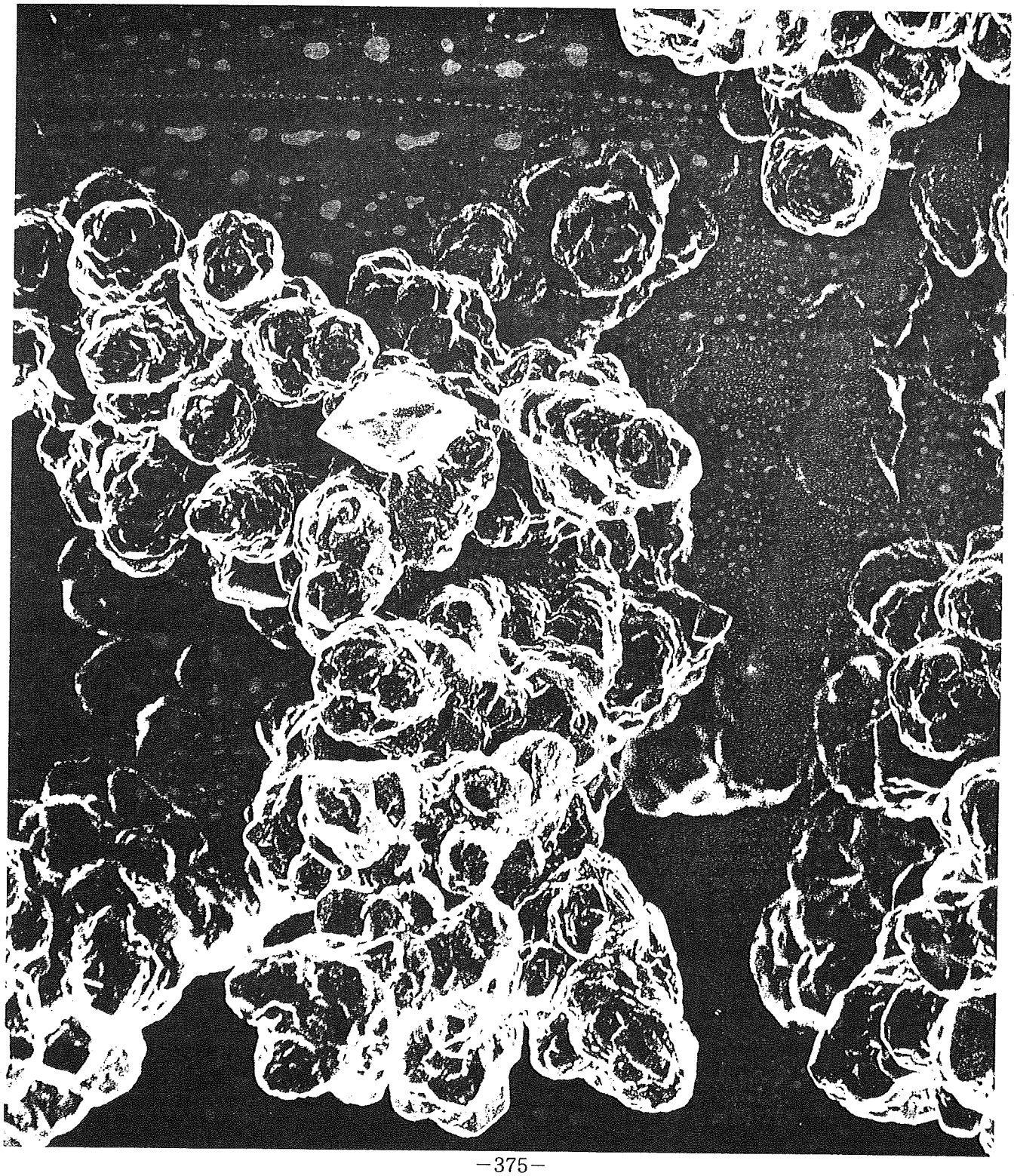
＜特集:大腸癌肝転移に対する治療＞



大腸癌肝転移に対する治療

大腸癌肝転移に対する手術療法

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はじめに

大腸癌肝転移に対する治療の第1選択が肝切除であることに異論はない。100例以上の症例を集積した報告で肝切除例の予後を見ると(表1)、症例集積期間はさまざまではあるが、報告年度が新しいものほど5年生存率は向上している。肝切除後の再発は残肝再発が40%、次いで肺転移が20%に見られる[1]。

肝切除後の予後不良因子(表2)として異論がないのは、剥離断端の癌露出、肝所属リンパ節転移陽性、衛星病変など肝転移進展因子陽性、肝外転移であり、さらに予後に大きく影響を与える因子として、肝転移個数、肝切除断端距離(tw)、肝転移切除後のCEA値とCA19-9値などが挙げられる。

本稿では、大腸癌肝転移に対する手術療法について現在の討議点を中心に解説する。

肝切除の適応

肝切除のstandard criteriaを表3に示す。肝転移症例のうち、切除可能なものは25～50%である[3]。

現在では肝以外の臓器に転移があっても、それが完全切除できれば肝転移、他臓器転移ともに切除することが多い。また、肝転移巣切除後の残肝再発についても初回手術と同じ基準で切除の対象となり、初回手術と同様の予後が期待できる。

肝切除に関する討議点

1) 切除時期

同時性肝転移に対しては、原発巣と同時に切除するものと、まず原発巣を切除して、その後3カ月ほど待って肝転移巣を切除するものとがある。

同時切除を行う理由は、①経過観察をしても予後に変わりはなく、②術前・術中の画像診断で小病巣も把握できるから遅らせる必要はない、③3カ月遅らせることで肝切除の時期を逃す、あるいは肝転移巣からの2次転移の危険性があるなどである。

異時切除を行う理由は、①肝転移状況や肝外転移の精査、②肝切除を同時に行うことによる死亡率や合併症率が高い、③同時に行うと微小転移を診断できないことがあるので、隠れた転移巣が明らかになるまで待って肝切除を行う、というものである。

原発巣切除は肝転移巣切除に先行して、あるいは同時に行われるのが一般的であるが、Menthaら[4]は、多発肝転移や大きな肝転移では原発巣手術後に肝転移巣が進展する危険性があるため、大腸癌の狭窄症状がない症例ではまずneoadjuvant chemotherapyを行い、6コース(肝転移奏効例では3コース)後にまず肝切除を行い、その3～8週後に原発巣の手術を行う方法を提唱している。

2) 肝転移個数と大きさから見た適応

一般に、単発例は多発例よりも予後が良く、転移個数の多いものはそれ以下のものと比べて予後は不良である。その理由は、転移個数が多いものでは切除断端距離を十分に取れないことが予後不良の理由ではないかと推測されている。腫瘍径が小さいもの、特に3cm以下のものはそれ以上のものと比べて予後は良い。一方、切除断端の距離(tw)を十分にとって切除すれば、転移個数や大きさは予後に関係しないとする報告も少なくない。

3) 切除断端距離(tw)

切除断端に癌が露出しているものの予後は不良である。さらに、切除断端が陰

表1 肝転移切除例の予後(報告例)

報告者	発表年	paper	症例数	集積期間	5年生存率(%)
Wilson SM	1976	Arch Surg 111	60		26
Adson MA	1984	Arch Surg 119	141		25
Hughes KS	1986	Surgery 100	607		33
Scheele J	1991	Surgery 110	266	1960-1988	31
Doci R	1991	Br J Surg 78	100	1980-1989	30
Gayowsky TJ	1994	Surgery 116	204	1981-1991	32
Noldlinger B	1996	Cancer 77	1568	1968-1990	28
Jamison RL	1997	Arch Surg 132	280		27
Fong Y	1997	J Clin Oncol 15	456	1985-1991	38
Beckurts KTE	1997	Br J Surg 84	126	1987-1994	14
Elias D	1998	Eur J Surg Oncol 24	269	1984-1996	34
Iwatsuki S	1999	J Am Coll Surg 189	305		32
Ambiru S	1999	Dis Colon Rectum 42	168	1984-1997	26
Fong Y	1999	Ann Surg 230	1001	1985-1998	37
Minagawa M	2000	Ann Surg 231	235	1980-1997	38
Sugihara K	2000	Ann Chirur Gynec 89	330	1985-1997	44
Belli G	2002	J Hepatobili Pancreat Surg 9	181	1986-2000	40
Choti MA	2002	Ann Surg 235	226	1984-1999	40
Kato T	2003	Dis Colon Rectum 46	585	1992-1996	39
Adam R	2006	Proc ASCO #3521	2122	1974-2004	42

性でもtwが10mm以下の症例の予後は不良とされ、twを10mm以上取ることは肝切除時の主要な目標であった。一方、肝転移巣周辺の衛星病変の頻度は少なく、存在する範囲も転移巣からわずかの距離であり、肝切除前の転移存在診断が確実に行えるようになった現在では、断端(−)であれば切除距離には関係しないとする報告も多い。

4) 肝切除術式と肝所属リンパ節郭清

肝切除術式は局所切除、区域切除、葉切除、拡大葉切除(3区域切除)などが行われ、大きく分けて、解剖学的肝系統切除と非解剖学的肝局所切除とに分類される。基本術式が解剖学的系統切除か非解剖学的部分切除かについては解決していない。

肝門部リンパ節転移は13〜25%[1,5]にみられ、他部位へ転移しているsignalであるとされる。その予後は不良で、現在では肝門部リンパ節転移例は手術適応外とすることが世界的なコンセンサスである。

転移陽性リンパ節郭清例の5生率は0〜42%[5]で、5年生存率は低いものの肝門部リンパ節郭清を行うことで生存期間が延長するという報告も多い。

予防的肝門部リンパ節郭清の評価は定まっていない。

表2　肝転移切除例の予後不良因子[2]

原発巣因子	肝転移巣因子
腹膜転移：P＋	H因子：H3（大腸癌取扱い規約6版）
組織型：por / muc	転移個数：＞4
壁深達度：si / ai	最大径：＞3cm
リンパ節転移：＞n3	転移巣の遺残：あり
リンパ節転移個数：＞4	tw≦10mm
ew：＋	肝門部リンパ節転移：あり
	肝転移進展因子陽性
肝転移治療前因子	門脈腫瘍塞栓、肝静脈腫瘍塞栓
転移時期：同時	胆管内腫瘍進展、隣接臓器浸潤
CEA・CA19-9 ＞ 正常値	肝内微小転移、神経周囲浸潤
CEA doubling time 短い	転移巣周囲皮膜形成なし
	Liver cell entrapment
	その他
	他臓器転移：あり
	肝切後CEA・CA19-9 ＞ 正常値

表3　肝切除のstandard criteria

・外科切除のriskが低い ・原発巣がコントロールされている ・適度な残肝量を残して転移巣が完全に切除できる ・肝転移以外の転移巣がない ・肝所属リンパ節転移がない
・肝転移個数が4個以下 ・切除断端のclear margin(tw)が10mm以上切除できる

切除不能肝転移例の対応

1) Neoadjuvant chemotherapy

Bismuthら[6]は、切除不能例に5-FU/folinic acid/oxaliplatin併用療法を先行し、腫瘍の縮小を待って局所的に根治切除が可能となった時点で肝切除を行った。53例中46例に肉眼的根治切除が行え、非治癒切除となった7例には、門脈塞栓術により残肝の増大を図り化学療法を続けて第2期切除を行った結果、5年生存率は40%、残肝再発66%、肝外再発47%と報告した。これ以後、切除不能例に対してneoadjuvant chemotherapyを行い，腫瘍の縮小が得られたものに切除を行う報告は多い。

2) 残肝量が少ない症例の対応

肝切除後の残肝容積が25%以下の場合90%が肝機能障害を起こし、慢性の肝疾患がある患者や大量の化学療法を受けた患者では40%以上の残肝量が要るとされる。そこで非腫瘍部の肝を40%以上温存できない場合には術前に片側の門脈塞栓術あるいは門脈結紮を行い予定残肝容積増大を促す適応となる。

3) Two stage operation

Bismuthら[6]およびAdamら[7]は、多発肝転移で切除不能と思われる症例に対して、術前化学療法、門脈塞栓術を行ってもone stageで完全切除ができない場合はtwo stage手術を提唱している。第Ⅰ期手術では、できるだけ多くの転移巣を切除して、残肝の肥大を待つ間全身化学

療法で遺残腫瘍の増大と転移を防ぎ、肝肥大が起きて完全切除ができるようになれば第Ⅱ期手術を行うものである。報告では、第Ⅰ期手術では無かった術死が15%にあり合併症もⅡ期手術では多い。

4）肝切除と凝固療法の併用

多発転移に対しては、ラジオ波凝固療法(RFA)と肝切除の併用が行われており、Curleyら[8]の報告では肝切除の5年生存率65%、肝切除とRFAの併用36%、RFA単独22%であった。注意しなくてはならないのは、併用療法が肝切除単独やRFA単独治療と比べて術後の合併症が20%前後と高く、手術死亡もあることである。

Eliasら[9]は、肝切除量が大きくなって残肝機能を維持できない21症例に対して、切除線上の転移巣をRFAで焼灼して壊死させ、その壊死部上で肝を切除し、小転移巣はRFAで焼灼した結果、術死の1例を除いて切離線上の局所再発はなかったと報告している。

また、肝切除の補助療法として断端陽性例、あるいはtwが10mm未満の症例に同部の凍結療法、マイクロ波凝固壊死療法やラジオ波熱凝固療法などの凝固療法を行う報告もある。

おわりに

大腸癌肝転移に対して治癒が期待できる治療は肝転移巣切除しかない。肝転移切除不能例に対しては、抗癌剤の肝動注療法あるいは全身化学療法を行うのが今までの治療戦略だった。現在の検討課題は、いかにして切除例の治癒度を高め、いかにして切除不能例を治癒切除が可能な状況にするかという点である

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特集 Stage IV 大腸癌と診断したらどうするか

肝転移を伴う Stage IV 大腸癌の治療方針

Treatment policy for stage IV colorectal cancer with liver metastases

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肝転移を伴うStage IV大腸癌では，まず原発巣の治癒切除を行い，次いで肝転移巣に対する治療を行う．

肝転移に対する治療は転移巣の完全切除が第一選択である．完全切除が行えない症例では切除と凝固療法を併用したり，neoadjuvant chemotherapyを行い腫瘍縮小を待って切除を行う．残肝量が少なくなる症例では門脈塞栓を行って肝肥大を，あるいは二期手術を計画して転移巣の切除を目指す．

切除以外では，ラジオ波や凍結などの凝固療法が有望である．外国では放射線外照射も行われる．

はじめに

当院における1965～1999年の大腸癌手術例は3,235例で，そのうち414例(12.3%)が肝転移のためにStage IVとなった．これは全Stage IV症例中の56%に当たる．同時期の治癒切除例2,491例の術後の再発でも肝転移再発が7.5%で最も多い再発であり，肝転移への対応は大腸癌治療の上で重要な位置を占める．

肝転移を伴うStage IV大腸癌に対する治療戦略は，原発巣が切除できるものは原発巣による症状があるものはもちろん，症状がないものについても持続する出血や将来おこるであろう狭窄を予防するためにまず原発巣を切除する．原発巣を切除して，遺残する転移巣を肝転移のみにすれば，肝切除を初めとする局所療法や全身化学療法などいろいろな治療法を選択できる．原発巣を切除できない症例に対しては全身化学療法を行う．

本稿では原発巣を切除した上での肝転移に対する局所療法について解説する．

I. 肝 切 除

1．肝転移切除の現状

肝転移無治療例では5年生存は期待できず[1)2)]，非切除例の5年生存率が5%以下であるのに対し，肝切除例の5生率は20%～50%[3)]で原発巣と

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Key words：大腸癌／肝転移／肝切除／凝固療法／切除不能肝転移の治療

表1　肝転移切除後の予後不良因子(文献4より)

1．原発巣因子	3．肝転移切除後の予後因子：手術因子
根治度　C	断端陽性
リンパ節転移陽性(転移個数多)	tw＜10 mm
組織型　低分化／粘液	肝転移巣の遺残
ly　2～3	
budding あり	4．肝転移切除後の予後因子：背景因子
	術前遠隔転移
2．肝転移巣因子	肝転移時の他臓器転移
肝転移組織型　低分化／粘液	同時性
肝転移個数(多発)	無病期間＜1年
局在(両葉)	肝切除前 CEA 高値
肝転移程度(H_3)*	肝切除後 CEA 高値
腫瘍最大径	肝切除後 CA19-9 高値
衛星病変あり	
肝転移進展因子	
門脈腫瘍塞栓，肝静脈腫瘍塞栓	
胆管内腫瘍進展，門脈浸潤	
神経周囲浸潤	
腫瘍周囲偽皮膜形成	
liver cell entrapment	
肉眼型	
肝所属リンパ節転移陽性	

*大腸癌取扱い規約第6版による

同様に外科的完全切除以外に根治的な治療法はない．現在では肝以外の臓器に転移があっても，それが完全切除できれば肝転移，他臓器転移ともに切除することが多い．

肝切除後の再発は残肝再発が40%，次いで肺転移が20%に見られて[4]，肝切除後はこの2つの再発の予防法が現在の課題である．

肝切除後の予後に関係する因子を表1に示した．切除後の予後不良因子として異論がないのは，剝離断端の癌露出，肝所属リンパ節転移陽性，衛星病変など肝転移進展因子陽性，肝外転移であり，さらに予後に大きく影響を与える因子として肝転移個数，肝切除断端距離(tw)，肝転移切除後のCEA値とCA19-9値などがあげられる．大腸癌取扱い規約第7版で新たに採用された肝転移の進行度分類における予後規定因子は，肝転移巣の転移個数と最大径および原発巣のリンパ節転移度である[3)5)]．

肝転移巣切除後の残肝再発についても根治の可能性があれば，初回手術と同じ基準で切除の対象となる．再肝切除の成績は5生率は30～50%[6)-9)]と良好であり再肝切除は肝転移の治療成績を向上させる重要な因子である．

2．肝切除の適応

肝切除の適応基準として，①外科切除のリスクが良いこと，②原発巣がコントロールされていること，③適度な残肝量を残して肝転移巣が完全に切除できること，④肝転移以外の遠隔転移がないこと，⑤肝所属リンパ節転移がないことが一般にあげられ，さらに肝転移巣の条件として，⑥肝転移個数4個以下，⑦切除断端距離(tw)を10 mm以上切除できることが手術のstandard criteriaとされてきた．肝転移症例のうち，切除可能なものは25～50%である[10)]．

以下，手術に関係するいくつかの問題点について考察する．

3．切除時期

同時性肝転移に対しては，原発巣と同時に切除する者と，まず原発巣を切除して，その後3ヵ月ほど待って肝転移巣を切除する者とがある．

同時切除を行う理由は，①経過観察をしても予後に変わりはなく，②術中超音波検査で小病巣も