J Gastrointest Surg (2012) 16:1888–1896
DOI 10.1007/s11605-012-1959-6

ORIGINAL ARTICLE

Concurrent Chemoradiotherapy Followed by Metastasectomy Converts to Survival Benefit in Stage IV Rectum Cancer

Jen-Kou Lin · Lin-Kun Lee · Wei-Shone Chen · Tzu-Chen Lin
Jeng-Kai Jiang · Shung-Haur Yang · Huann-Sheng Wang
Shih-Ching Chang · Yuan-Tzu Lan · Chun-Chi Lin · Chueh-Chuan Yen
Jin-Hwang Liu · Cheng-Hwai Tzeng · Hao-Wei Teng

Received: 20 March 2012 / Accepted: 28 June 2012 / Published online: 26 July 2012

Abstract
Background To investigate the impact of concurrent chemoradiotherapy (CCRT) on stage IV rectum cancer.
Methods Between 2000 and 2011, 297 consecutive patients diagnosed with stage IV rectum cancer (synchronous metastasis) were enrolled. Cox proportional hazard analyses were used for prognostic factors determination, and the Kaplan–Meier method was used for survival analyses. Propensity scores with the one-to-one nearest-neighbor matching model were used to select matched patients for validation studies.
Results In total, 63 patients received CCRT and 234 did not. The patients in the CCRT group were younger, had more low-lying lesions, and had more T4 lesions, lung metastases, metastasectomies, and oxaliplatin-based upfront chemotherapy. Before propensity-score matching, a younger age (HR=0.662, P=0.016), lower carcinoembryonic antigen (CEA) level (≤20 ng/ml) (HR=0.531, P=0.001), no metastasectomy (HR=3.214, P<0.001), and no CCRT (HR=1.844, P=0.019) were independent prognostic factors after controlling for other confounding factors. After matching, only CEA and metastasectomy, but not CCRT, were independent prognostic factors. The survival benefit of CCRT was restricted to patients who undergo subsequent metastasectomy.
Conclusions Upfront CCRT only provided a survival benefit in patients with stage IV rectum cancer who undergo subsequent metastasectomy.

Jen-Kou Lin and Lin-Kun Lee contributed equally to this study.

Grant support: The Division of Experimental Surgery of the Department of Surgery, Taipei Veterans General Hospital and by the Taipei Veterans General Hospital, Taiwan Clinical Oncology Research Foundation, Department of Health, Taiwan.

L.-K. Lee · C.-C. Yen · J.-H. Liu · C.-H. Tzeng · H.-W. Teng (✉)
Division of Hematology and Oncology, Department of Medicine,
Taipei Veterans General Hospital,
No.201, Sec. 2, Shih-Pai Road,
Taipei 112, Taiwan
e-mail: danny_teng@yahoo.com.tw

H.-W. Teng
Institute of Clinical Medicine, National Yang-Ming University,
Taipei, Taiwan

J.-K. Lin · L.-K. Lee · W.-S. Chen · T.-C. Lin · J.-K. Jiang · S.-H. Yang · H.-S. Wang · S.-C. Chang · Y.-T. Lan · C.-C. Lin · C.-C. Yen · J.-H. Liu · C.-H. Tzeng · H.-W. Teng
School of Medicine, National Yang-Ming University,
Taipei, Taiwan

J.-K. Lin · W.-S. Chen · T.-C. Lin · J.-K. Jiang · S.-H. Yang · H.-S. Wang · S.-C. Chang · Y.-T. Lan · C.-C. Lin
Division of Colon and Rectum Surgery, Department of Surgery,
Taipei Veterans General Hospital and National Yang-Ming University,
Taipei, Taiwan

Keywords Colorectal cancer · Metastases · Propensity score model · Radiation

Introduction

Colorectal cancer is the third most common malignancy worldwide and the leading malignancy in Taiwan. One third of cases are of rectum cancer. Unfortunately, one quarter of rectum cancer cases are of metastatic rectum cancer (stage IV) in Taiwan (Department of Health, Executive Yuan 2008).[1] Despite advances in multiple-modality treatment, the median overall survival (OS) of patients with stage IV rectum cancer is only around 20–28 months.[2–6]

The optimal treatment strategy in stage IV rectum cancer remains unclear, and most recommendations are based on extrapolation from metastatic colon cancer and stage II–III rectum cancer. According to the National Comprehensive Cancer Network (NCCN) guidelines (V1. 2012), upfront systemic chemotherapy followed by concurrent chemoradiotherapy (CCRT) or not and upfront CCRT followed by systemic chemotherapy are considered equal by consensus; no treatment strategy is better than another. Data to guide decisions regarding the optimal approach in this population were limited until now.

Pre-operative (pre-op) CCRT is the standard of care for patients with stage II–III rectum cancer. Advancements include significant improvement in local control and sphincter preservation, as reported in the German CAO/ARO/AIO Rectum Cancer Trial.[7] In clinical practice, physicians often incorporate CCRT into the treatment plan of patients with stage IV rectum cancer. However, as we know, CCRT only decreases local recurrence; it does not improve OS in stage II–III rectum cancer,[8] and no trials have evaluated the efficacy of CCRT in stage IV rectum cancer.

We conducted a retrospective study to examine the impact of upfront CCRT on OS in patients with stage IV rectum cancer. All patients with stage IV rectum cancer had synchronous metastasis. We aimed to identify the potential subpopulation who obtained a survival benefit after upfront CCRT followed by systemic chemotherapy in order to avoid unnecessary adverse events of CCRT in those patients who will not benefit.

Materials and Methods

Study Population and Data Collection

This cohort study retrospectively reviewed patients with clinical stage IV (metastatic) rectum cancer who underwent CCRT or did not undergo CCRT in Taipei Veterans General Hospital from January 2000 to September 2011. Rectum cancer was defined as a cancerous lesion located within 15 cm of the anal verge.[9] The inclusion criteria was rectum cancer with solitary or multiple metastasis proved by pathology (primary or metastatic lesion, type: adenocarcinoma) and imaging studies (computed tomography, magnetic resonance imaging, or positron emission tomography/computed tomography (CT)). Finally, 297 patients were enrolled. Tumors were staged according to the American Joint Committee on Cancer Staging system, 6th edition. The general characteristics and clinicopathological staging of patients were obtained from a computer database containing detailed information of all patients, including the pathological type and treatment modality. Follow-up information and survival data were obtained from hospital records. Follow-up was continued until October 2011 or the time of death. Patients were followed up at 3-month intervals from the time of diagnosis for the first 2 years and then at 6-month intervals for 5 years and thereafter, annually. Examinations at follow-up included physical examination, rectodigital examination, carcinoembryonic antigen (CEA, in nanograms per milliliter) levels, chest X-rays, and abdominal CT scans. Decisions regarding resection of metastatic lesions in both groups were made on an individual patient basis according to the patient's will, at the discretion of the attending physicians, and according to resectability as evaluated by surgeons and radiologists.

The upfront chemotherapy was determined by the attending physicians including a medical oncologist and a surgical oncologist. The complex cases warranting metastasectomy were discussed in multidisciplinary conference in the presence of colorectal, liver, and lung surgeons; radiologists; medical oncologists; radiation oncologists; and pathologists. The standard systemic chemotherapy we used included 5-fluorouracil (5-FU)/leucovorin/oxaliplatin (FOLFOX4/FOLFOX6), 5-FU/leucovorin/irinotecan (FOLFIRI), and 5-FU/leucovorin (HDFL/DeGramont), and cetuximab or bevacizumab was used with one of above regimens. Cetuximab was used in patients with the wild-type *KRAS* gene (codons 12 and 13). Palliation meant that the patient refused chemotherapy, and not available (n.a.) meant that the patient received treatment in another hospital and we obtained the survival status by telephone.

In the CCRT group, all patients had the primary lesion located $\leq$12 cm from anal verge. The "sandwich" approach was as follows: an upfront systemic chemotherapy 1–2 courses, followed by CCRT (in which the chemotherapy was the same as the upfront chemotherapy, with a dose intensity of around 80–100% individually) and continuation of the same chemotherapy. The radiation dosage was 45–50 Gy in 25–28 fractions to the pelvis (long-course CCRT).[10]

Statistical Analysis

The Kaplan–Meier method was used for survival analysis, and cancer-specific mortality was the event used for OS analysis. Patients who remained alive at the end of the follow-up period were censored. OS was defined as the time

from diagnosis of rectum cancer to death from cancer. The cause of death was determined by the primary physicians or by a review of the medical chart.

Categorical variables were compared using the χ^2 test between patients who received CCRT and those who did not. The Cox proportional hazards model was applied for univariate and multivariate analyses to determine the prognostic influence of clinicopathological factors and CCRT on survival endpoints.

Propensity scores were used to control for selection bias [11] and derived using binary logistic regression to generate a propensity score for each patient who underwent CCRT or did not. The variables entered in the propensity model were age, gender, pathology, location (distance from anal verge, ≤7 or >7 cm), pre-op T, N, M stage, CEA level, metastasectomy, and upfront chemotherapy regimens. Subsequently, a one-to-one match between patients who received CCRT and those who did not receive CCRT was obtained using the nearest-neighbor matching method.[11]

A P value<0.05 was regarded as statically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 16.0 for Windows; SPSS Inc, Chicago, IL).

Results

Baseline Clinical Characteristics

In total, 297 patients with stage IV rectum cancer were enrolled. The baseline demographic data are shown in Table 1. Sixty-three (21.2%) patients received CCRT, and 234 (78.8%) patients did not receive CCRT. The patients in the non-CCRT group were older than those in the CCRT group (P=0.010). In both groups, there was a male predominance, with a similar male-to-female ratio. The pathology in both groups was mainly adenocarcinoma (93.6% in the CCRT group and 92.0% in the non-CCRT group), with a few cases of mucinous adenocarcinoma, signet ring cell carcinoma, and carcinoma. The location of the tumor in the non-CCRT group was mainly at a distance >7 cm from the anal verge (66.7%), whereas in CCRT group the location of the tumor was mainly at a distance ≤7 cm from the anal verge (73.0%) (P<0.001). The pre-op T stage in the CCRT group contained more T4 lesions than the non-CCRT group (38.1% vs. 23.1%, P=0.016). A similar frequency of pre-op N2 status was noted in both groups (56.8% vs.

Table 1 Comparison of the baseline demographics of patients with stage IV rectum cancer who underwent CCRT or did not undergo CCRT

Total, N=297		No CCRT, n=234 (%)	CCRT, n=63 (%)	P value
Age (years)	≤70	133 (56.8)	47 (74.6)	0.010*
	>70	101 (43.2)	16 (25.4)	
Gender	Male	171 (73.1)	44 (69.8)	0.610
	Female	63 (26.9)	19 (30.2)	
Pathology	Adenocarcinoma	219 (93.6)	58 (92.0)	0.335
	Mucinous adenocarcinoma	9 (3.8)	5 (8.0)	
	Signet cell carcinoma	4 (1.7)	0 (0.0)	
	Carcinoma	2 (0.9)	0 (0.0)	
Distance from anal verge (cm)	>7	156 (66.7)	17 (27.0)	<0.001*
	≤7	78 (33.3)	46 (73.0)	
Pre-op T	Non-T4	180 (76.9)	39 (61.9)	0.016*
	T4	54 (23.1)	24 (38.1)	
Pre-op N	N 0-1	101 (43.2)	24 (38.1)	0.470
	N2	133 (56.8)	39 (61.9)	
Pre-op M	Liver	142 (60.7)	31 (49.2)	0.040*
	Lung	28 (11.9)	16 (25.4)	
	Liver and lung	25 (10.7)	4 (6.4)	
	Others	39 (16.7)	12 (19.0)	
CEA (ng/ml)	≤20	81 (34.6)	29 (46.0)	0.096
	>20	153 (65.4)	34 (54.0)	
Metastasectomy	Without	176 (75.2)	39 (61.9)	0.036*
	With	58 (24.8)	24 (38.1)	
Upfront regimen	Bevacizumab-based	11 (4.7)	1 (1.6)	<0.001*
	Cetuximab-based	7 (3.0)	8 (12.7)	
	Oxaliplatin-based	90 (38.5)	40 (63.5)	
	Irinotecan-based	33 (14.1)	1 (1.6)	
	5-FU-based	24 (10.3)	13 (20.6)	
	Palliation	41 (17.5)	0 (0)	
	n.a.	28 (11.9)	0 (0)	

CCRT concurrent chemoradiotherapy, *CEA* carcinoembryonic antigen, *CT* chemotherapy, *n.a.* not available, *pre-op* preoperative, *5-FU* 5-fluorouracil

*P<0.05

61.9%, P=0.470). Pre-op liver metastasis was more common in the non-CCRT group than in the CCRT group (60.7% vs. 49.2%, P=0.040). The CEA distribution (CEA> 20 ng/ml) was similar (65.4% vs. 54.0%, P=0.096) in both groups. Fewer patients in the non-CCRT group underwent metastasectomy than in the CCRT group (24.8% vs. 38.1%, P=0.036). Eighty-two patients underwent metastasectomy: five who received CCRT only and 77 who underwent surgery for the primary tumor and metastasectomy (60 patients underwent concurrent resection of the primary and metastatic tumors, while 17 underwent sequential resection of the primary and metastatic tumors). Palliative treatment was common in the non-CCRT group, and the most commonly used upfront chemotherapy was an oxaliplatin-based regimen, especially in the CCRT group (P<0.001).

Factors Associated with OS

For the whole population (stage IV rectum cancer), the median OS was 21.3 months. One hundred fifty-six patients died, and 141 patients were still alive for their last follow-up visit. The median survival in the non-CCRT group was 19.5 months, and the median survival in the CCRT group was 37.4 months (Fig. 1a, P=0.004). Among the 234 patients who did not receive CCRT, 136 (58.1%) died during the follow-up period. Of the 63 patients who underwent CCRT, 20 (31.7%) died.

An older age (>70 years), higher location of the tumor (>7 cm from the anal verge), advanced pre-op N stage (N2), higher CEA level (>20 ng/ml), no metastasectomy, and no CCRT were found to be associated with poor overall survival by univariate analysis (Table 2). In multivariate analysis, only a younger age (HR=0.662, P=0.016), lower CEA level (≤20 ng/ml) (HR=0.531, P=0.001), no metastasectomy (HR=3.214, P<0.001), and no CCRT (HR=1.844, P=0.019) were found to be independent prognostic factors that influenced overall survival after controlling for other confounding factors (Table 2).

Figure 1b, c shows the impact of upfront chemotherapy on OS. The median survival for bevacizumab/cetuximab, oxaliplatin/irinotecan, 5-FU, no chemotherapy, and n.a was 27.1, 27.0, 20.5, 7.5, and 10.6 months, respectively (P< 0.001) (Fig. 1b). However, after excluding the group that did not undergo chemotherapy and the data n.a. group, there was no difference in OS between the different upfront regimens of bevacizumab/cetuximab vs. oxaliplatin/irinotecan vs. 5-FU, P=0.342) (Fig. 1c).

According to the RECIST criteria, we subdivided the patients in the CCRT group into two subgroups: responders (at least partial remission; n=37) and non-responders (stable or progressing disease; n=26). The overall median survival of the non-responders was 23.5 months; the same could not be calculated in the responders because most patients in this group were still alive (P=0.067).

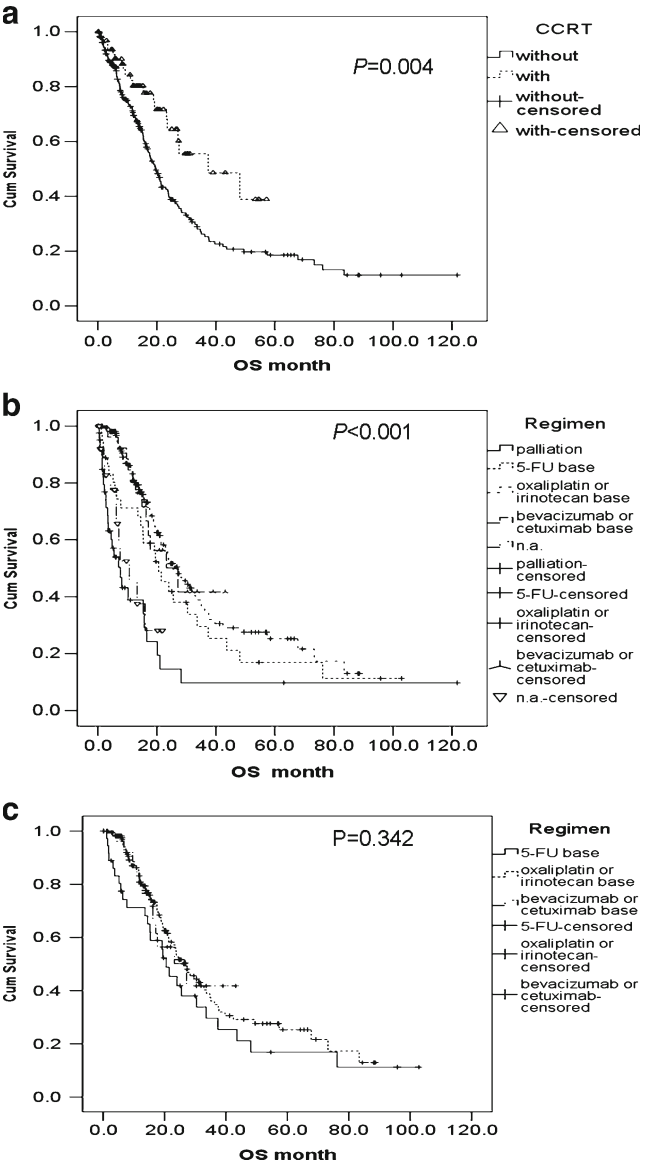

Fig. 1 **a** Overall survival (OS) of patients with stage IV rectum cancer by concurrent chemoradiotherapy (CCRT) status. **b**, **c** OS of patients with stage IV rectum cancer by chemotherapy regimen: **b** palliation, 5-flurouracil (5-FU), oxaliplatin/irinotecan, bevacizumab/cetuximab, and not available (n.a.), and **c** 5-FU, oxaliplatin/irinotecan, and bevacizumab/cetuximab

Factors Associated with OS After Propensity Score Correction with the One-to-One Nearest-Neighbor Matching Method

A severe discrepancy in the upfront chemotherapy was present between the two groups. In the non-CCRT group, 11 patients (4.7%) received bevacizumab vs. 1 (1.6%) in the CCRT group; 33 patients (14.1%) in the non-CCRT group received irinotecan vs. 1 (1.6%) in the CCRT group; and 69 patients (29.4%) in the non-CCRT group received palliation or n.a. vs. 0 (0.0%) in the CCRT group. These patients were

Table 2 Prognostic factors for survival in patients with stage IV rectum cancer according to univariate and multivariate analyses in the Cox proportional hazards model

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age ≤70 vs. >70 years	0.692	0.502~0.954	0.025*	0.662	0.473~0.927	0.016*
Distance from anal verge (cm) >7 vs. ≤7 cm	1.439	1.034~2.002	0.031*	0.973	0.680~1.392	0.882
Pre-op T T4 vs. non-T4	0.720	0.507~1.022	0.066	0.705	0.484~1.028	0.069
Pre-op N N2 vs. N0-1	1.415	1.027~1.949	0.034*	1.369	0.981~1.911	0.065
CEA (ng/ml) ≤20 vs. >20	0.429	0.304~0.607	<0.001*	0.531	0.370~0.763	0.001*
Metastasectomy Without vs. with	3.989	2.577~6.174	<0.001*	3.214	2.047~5.044	<0.001*
CCRT Without vs. with	1.954	1.220~3.128	0.005*	1.844	1.107~3.071	0.019*

CCRT concurrent chemoradiotherapy, *CEA* carcinoembryonic antigen, *pre-op* pre-operative

*$P<0.05$

excluded from this study initially (Fig. 2a). Subsequently, propensity analysis with the one-to-one nearest-neighbor matching method was applied to minimize the confounding factors including age, gender, pathology, tumor location (distance from the anal verge), pre-op T, pre-op N, pre-op M, CEA level, metastasectomy, and upfront chemotherapy (Fig. 2a). Finally, 40 patients were matched in each group, and the abovementioned factors appeared to be well-matched between these two groups (Table 3). After matching, under univariate and multivariate analysis, only a higher CEA level (>20 ng/ml) and no metastasectomy were found to be associated with poor OS, but not CCRT (Table 4) (Fig. 2b, $P=0.501$). In subgroup analysis, patients who underwent CCRT followed by metastasectomy had a superior survival curve as compared with patients who received CCRT without undergoing subsequent metastasectomy or patients who did not receive CCRT (Fig. 2c, $P=0.025$). The median OS in the non-CCRT group was 25.5 months, while that in the CCRT group who did not undergo resection of metastatic lesions was 18.9 months. No median survival data were obtained for the CCRT group who underwent resection of metastatic lesions because only two of ten patients died during the period of follow-up. In contrast, the CEA level did not have an impact on the OS of patients who underwent CCRT (Fig. 2d, $P=0.690$). Then, in order to validate the potential benefits of CCRT in stage IV rectum cancer patients who underwent subsequent metastasectomy (Fig. 2c), we selected stage IV rectum cancer patients who underwent metastasectomy and applied propensity analysis with the one-to-one nearest-neighbor matching method to minimize the confounding factors previously mentioned, with the exception of CCRT. Eighteen patients were selected in each group (with or without CCRT) (Fig. 2e). We found that the patients in the CCRT group still had a superior survival curve as compared with the patients in the non-CCRT group (Fig.2f, $P=0.037$).

Complications After Surgical Resection of the Primary Rectal Tumor

The incidence of treatment mortality (death within 30 days of operation) was 11/266 (4.1%). Complications after resection of the primary rectal tumor included myocardial infarction (1/266), atelectasis of the lungs (3/266), pulmonary embolism (1/266), pneumonia (5/266), respiratory failure (6/266), sputum impaction (1/266), pneumothorax (1/266), postoperative jaundice (1/266), renal failure (1/266), stress ulcer with upper gastrointestinal bleeding (4/266), deep vein thrombosis (1/266), wound infection (30/266), wound disruption (5/266), urinary tract infection (12/266), urinary retention (urinary catheterization>2 weeks) (6/266), intra-abdominal abscess (3/266), anastomotic bleeding (2/266), anastomotic leakage (23/266), intestinal obstruction (1/266), and stomal complication (3/266). The complications did not influence the subsequent chemotherapy schedule.

Discussion

The optimal treatment strategies for patients with stage IV rectum cancer are difficult to determine. In clinical practice, medical, surgical, and radiation oncologists often arrange

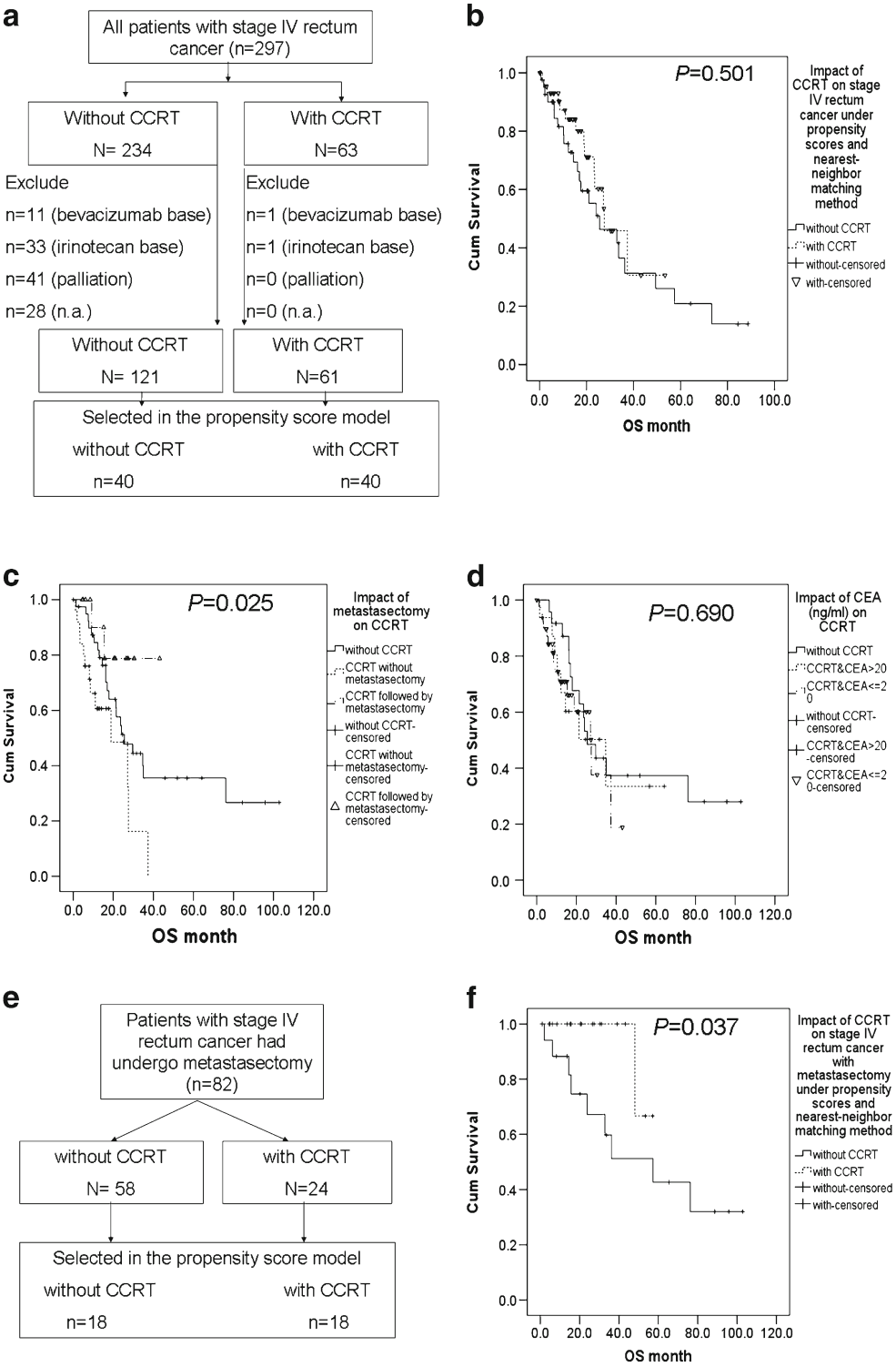

Fig. 2 **a** In all, 234 patients did not undergo CCRT, and 63 patients underwent CCRT. Patients who received upfront chemotherapy with irinotecan, bevacizumab, and those undergoing palliation or with data not available (n.a.) were excluded initially. Subsequently, 40 pairs of matched patients were selected for analysis by the propensity score model using the one-to-one nearest-neighbor matching method to minimize the confounding factors previously mentioned, with the exception of CCRT. **b** Forty patients were selected in each group (with or without CCRT), and CCRT did not provide a survival benefit in the stage IV rectum cancer patients. **c** In subgroup analysis, CCRT provided a survival benefit only in stage IV rectum cancer patients who underwent subsequent metastasectomy. **d** In subgroup analysis, a low CEA level did not have the impact on CCRT. **e** To validate the findings shown in **c**, we selected stage IV rectum cancer patients who underwent metastasectomy and applied propensity analysis and the one-to-one nearest-neighbor matching method to minimize the confounding factors previously mentioned, with the exception of CCRT. Eighteen patients were selected in each group (with or without CCRT). **f** We found that stage IV rectum cancer patients who underwent metastasectomy in the CCRT group still had a superior survival curve as compared with those patients who did not undergo CCRT

CCRT for patients with stage IV rectum cancer in addition to systemic chemotherapy. In the NCCN guidelines (V 1. 2012), radiotherapy is advised to be considered in highly selected cases in which patients have a limited number of liver or lung metastases (category 3 recommendation) or in the setting of a clinical trial.[12,13] It seems reasonable that CCRT is incorporated into the treatment strategy in cases of potentially curable stage IV rectum cancer to strengthen local control, but there are no definite indications and no randomized trials to prove the efficacy of CCRT in this population. To our knowledge, our retrospective analysis is the first large-scale study in the literature to examine the role of CCRT in stage IV rectum cancer. We found that CCRT followed by metastasectomy could improve the OS in

Table 3 Comparison of the baseline demographics of patients with stage IV rectum cancer who underwent CCRT or who did not in the propensity score model

Total, N=80		Without CCRT, n=40 (50%)	CCRT, n=40 (50%)	P value
Age (years)	≤70	28 (70.0)	28 (70.0)	1.000
	>70	12 (30.0)	12 (30.0)	
Gender	Male	27 (67.5)	28 (70.0)	0.809
	Female	13 (32.5)	12 (30.0)	
Pathology	Adenocarcinoma	39 (97.5)	38 (95.0)	0.556
	Mucinous adenocarcinoma	1 (2.5)	2 (5.0)	
Distance from anal verge (cm)	>7	17 (42.5)	16 (40.0)	0.820
	≤7	23 (57.5)	24 (60.0)	
Pre-op T	Non-T4	27 (67.5)	26 (65.0)	0.813
	T4	13 (32.5)	14 (35.0)	
Pre-op N	N 0-1	23 (57.5)	26 (65.0)	0.491
	N2	17 (42.5)	14 (35.0)	
Pre-op M	Liver	18 (45.0)	23 (57.5)	0.204
	Lung	13 (32.5)	5 (12.5)	
	Liver and lung	3 (7.5)	4 (10.0)	
	Others	6 (15.0)	8 (20.0)	
CEA (ng/ml)	≤20	24 (60.0)	16 (40.0)	0.074
	>20	16 (40.0)	24 (60.0)	
Metastasectomy	Without	24 (60.0)	26 (65.0)	0.644
	With	16 (40.0)	14 (35.0)	
Upfront regimen	Cetuximab-based	3 (7.5)	3 (7.5)	1.000
	Oxaliplatin-based	27 (67.5)	27 (67.5)	
	5-FU-based	10 (25.0)	10 (25.0)	

CCRT concurrent chemoradiotherapy, *CEA* carcinoembryonic antigen, *n.a.* not available, *pre-op* pre-operative, *5-FU* 5-fluorouracil

*P<0.05

patients with stage IV rectum cancer. The CCRT did not improve the OS in patients with ultimately unresectable stage IV rectum cancer and should be omitted to avoid unnecessary adverse events of CCRT.

In our population, CCRT was prone to be performed in patients of a younger age, T4 lesions, low-lying lesions, and those with non-disseminated metastasis (Table 1). This strategy is largely based on extrapolation from CCRT in stage II–III rectum cancer and limited stage IV colon cancer analysis, and this concept is used in clinical practice worldwide.[7,8,14–16] In our study, age, CEA, metastasectomy, and CCRT were found to be significant prognostic markers according to multivariate analyses in the Cox proportional hazards model, but not the location of the primary tumor, pre-op clinical T, and N. The significant survival benefit of CCRT obtained by the selection bias in patients undergoing CCRT that were younger and had less-disseminated metastasis, aggressive chemotherapy, and more metastasectomies

Table 4 Prognostic factors for survival in patients with stage IV rectum cancer according to univariate and multivariate analyses in the propensity score model

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age, ≤70 vs. >70 years	0.552	0.283~1.074	0.080	0.832	0.360~1.922	0.666
Distance from anal verge (cm), >7 vs. ≤7 cm	0.957	0.492~1.863	0.898	0.952	0.467~1.940	0.892
Pre-op T, T4 vs. non-T4	0.939	0.477~1.847	0.855	0.965	0.434~2.145	0.930
Pre-op N, N2 vs. N0-1	0.131	0.586~2.183	0.713	1.505	0.679~3.332	0.314
CEA (ng/ml), ≤20 vs. >20	0.425	0.217~0.834	0.013*	0.414	0.188~0.909	0.028*
Metastasectomy, without vs. with	3.621	1.632~8.037`	0.002*	3.031	1.259~7.296	0.013*
CCRT, without vs. with	0.793	0.404~1.560	0.502	1.113	0.542~2.284	0.771
Regimen, 5-FU-based vs. oxaliplatin-based vs. cetuximab-based	1.220	0.887~1.679	0.221	1.358	0.900~2.048	0.144

CCRT concurrent chemoradiotherapy, *CEA* carcinoembryonic antigen, *pre-op* pre-operative, *5-FU* 5-fluorouracil

*P<0.05

(Fig. 1a and Tables 1 and 2). Our results were similar to those of the retrospective studies of Radu et al.[17] They found that patients with stage IV rectum cancer who underwent CCRT followed by systemic chemotherapy and surgery or not have a better OS than patients undergoing palliative chemotherapy alone (contraindication to CCRT due to being more elderly or having more comorbidities). The impact of CCRT could not be assessed due to the small population size (n=22) and the heterogeneous characteristics in their study. The above results encouraged us to assess the actual impact of CCRT on stage IV rectum cancer using the propensity score model (Table 3 and Fig. 2a). However, we found that only metastasectomy and CEA but not CCRT were independent prognostic markers in the propensity score model (Table 4). This observation is partially supported by previous studies, which have indicated that CCRT reduces local recurrence only in stages II and III rectum cancer.[7,16,18] Furthermore, we examined the impact of metastasectomy and CEA on CCRT (Fig. 2c, d). Interestingly, in the subgroup analysis, only CCRT followed by metastasectomy improved the OS in patients with stage IV rectum cancer, and CCRT without sequential metastasectomy did not improved the OS (Fig. 2c). As we know, metastasectomy is the standard treatment for resectable or potentially resectable metastatic or recurrent colorectal cancer. The 5-year survival rate in patients after metastasectomy is around 50% worldwide.[19–21] It appears that upfront chemotherapy eradicates the micrometastasis, CCRT reduces local recurrence, and macrometastasis is eradicated by metastasectomy. This multiple-modality approach results in the greatest survival benefit in stage IV rectum cancer patients. Based upon our findings and previous reports,[17] we propose a new theoretical concept that CCRT should be used in cases of resectable or convertible stage IV rectum cancer, and CCRT should be omitted to avoid adverse events of CCRT in ultimately unresectable patients.

With respect to the dose intensity of chemotherapy during a long course of CCRT, the systemic chemotherapy dose was reduced by around 0–20% in our study, which was similar to previous reports.[15] The adverse events have been manageable in our experience.

There were some limitations in our analysis. First, our results were based on oxaliplatin and/or cetuximab, not irinotecan, and the impact of irinotecan and bevacizumab on CCRT was therefore not able to be assessed. Second, short-course radiotherapy (RT) was not performed, and we were therefore unable to compare long-course CCRT with short-course RT in patients with stage IV rectum cancer.[8,17,22] Long-course CCRT or short-course RT with or without delayed surgery is best reserved for patients whose cancers respond to systemic chemotherapy. The advantage of this strategy includes avoiding unnecessary adverse events of RT and maintaining the dose intensity of systemic chemotherapy.[17,22,23]

Conclusions

The role of CCRT in stage IV rectum cancer continues to evolve. CCRT only provided a survival benefit in stage IV rectum cancer patients who underwent subsequent metastasectomy in our study. We suggest that CCRT is restricted to cases of resectable and potentially convertible stage IV rectum cancer after effective upfront systemic chemotherapy and is followed by metastasectomy if possible.

Acknowledgments The authors wish to thank Cheng-Hwai Tzeng and Dr. Po-Min Chen for help in discussions regarding the data.

Conflicts of interest The authors have no conflicts of interest to disclose.

References

1. Naishadham D, Lansdorp-Vogelaar I, Siegel R, Cokkinides V, et al.: State disparities in colorectal cancer mortality patterns in the United States. Cancer Epidemiol Biomarkers Prev 2011;20:1296-1302.
2. Cunningham D, Humblet Y, Siena S, Khayat D, et al.: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.
3. Falcone A, Ricci S, Brunetti I, Pfanner E, et al.: Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25:1670-1676.
4. Montagnani F, Chiriatti A, Turrisi G, Francini G, et al.: A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: improved efficacy at the cost of increased toxicity. Colorectal Dis 2011;13:846-852.
5. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, et al.: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019.
6. Souglakos J, Androulakis N, Syrigos K, Polyzos A, et al.: FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer 2006;94:798-805.
7. Sauer R, Becker H, Hohenberger W, Rodel C, et al.: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
8. Minsky BD: Counterpoint: long-course chemoradiation is preferable in the neoadjuvant treatment of rectal cancer. Semin Radiat Oncol 2011;21:228-233.
9. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, et al.: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646.
10. Madoff RD: Chemoradiotherapy for rectal cancer—when, why, and how? N Engl J Med 2004;351:1790-1792.
11. D'Agostino RB, Jr.: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-2281.
12. Hong TS, Ritter MA, Tome WA, Harari PM: Intensity-modulated radiation therapy: emerging cancer treatment technology. Br J Cancer 2005;92:1819-1824.

13. Meyer J, Czito B, Yin FF, Willett C: Advanced radiation therapy technologies in the treatment of rectal and anal cancer: intensity-modulated photon therapy and proton therapy. Clin Colorectal Cancer 2007;6:348-356.
14. Bosset JF, Collette L, Calais G, Mineur L, et al.: Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123.
15. Sebag-Montefiore D: Developments in the use of chemoradiotherapy in rectal cancer. Colorectal Dis 2006;8 Suppl 3:14-17.
16. Gerard JP, Conroy T, Bonnetain F, Bouche O, et al.: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620-4625.
17. Radu C, Berglund A, Pahlman L, Glimelius B: Short-course preoperative radiotherapy with delayed surgery in rectal cancer—a retrospective study. Radiother Oncol 2008;87:343-349.
18. Bosset JF, Calais G, Mineur L, Maingon P, et al.: Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. J Clin Oncol 2005;23:5620-5627.
19. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, et al.: Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-766.
20. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, et al.: Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241:715-722, discussion 722-714.
21. Bartlett DL, Berlin J, Lauwers GY, Messersmith WA, et al.: Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1284-1292.
22. Shin SJ, Yoon HI, Kim NK, Lee KY, et al.: Upfront systemic chemotherapy and preoperative short-course radiotherapy with delayed surgery for locally advanced rectal cancer with distant metastases. Radiat Oncol 2011;6:99.
23. Fernandez-Martos C, Pericay C, Aparicio J, Salud A, et al.: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.