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Original Article

Continuing anti-EGFR monoclonal antibody after secondary resection significantly prolongs overall survival for patients with metastatic colorectal cancer who were responsive to first-line anti-EGFR monoclonal antibody plus chemotherapy doublet

Yao-Yu Hsieh[1,2,3,4], Yu-Li Su[5], Feng-Che Kuan[6], Shu-Chuan Grace Chen[7], Chia-Lun Chang[8,9], Yu-Yun Shao[10,11,12,13], Ching-Wen Tsai[14], Yi-Hsin Liang[10,11,12,13]

[1]Division of Hematology and Oncology, Taipei Medical University Shuang Ho Hospital, New Taipei 23561, Taiwan; [2]Division of Hematology and Oncology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan; [3]Taipei Cancer Center, Taipei Medical University, Taipei 11031, Taiwan; [4]TMU and Affiliated Hospitals Pancreatic Cancer Groups, Taipei Medical University, Taipei 11031, Taiwan; [5]Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, College of Medicine, Kaohsiung 83301, Taiwan; [6]Department of Hematology and Oncology, Chang Gung Memorial Hospital, Chiayi 61363, Taiwan; [7]Department of Mathematics and Statistics, Idaho State University, 921 South 8th Avenue, Pocatello, ID 83209-8085, USA; [8]Department of Hemato-Oncology, Wan Fang Hospital, Taipei Medical University, Taipei 11031, Taiwan; [9]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan; [10]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei 10051, Taiwan; [11]Center of Genomic and Precision Medicine, National Taiwan University College of Medicine, Taipei 10051, Taiwan; [12]Department of Oncology, National Taiwan University Hospital, Taipei 10002, Taiwan; [13]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei 10002, Taiwan; [14]Office of Data Science, Taipei Medical University, Taipei 11031, Taiwan

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Abstract: The combination of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAb) and doublet chemotherapy is the standard first-line treatment for patients with wild-type *RAS/BRAF* metastatic colorectal cancer (mCRC). Some patients may require secondary resection after first-line treatment. However, it remains unclear whether targeted therapy should be continued after liver resection. To investigate whether targeted therapy can be spared after secondary resection, we retrospectively analyzed data from the Taiwan National Health Insurance Research Database for patients with wild-type *KRAS* mCRC who received first-line anti-EGFR mAb plus doublet chemotherapy. Between 2013 and 2018, 5694 mCRC patients were screened, with 174 meeting the eligibility criteria and being enrolled in this study. Among them, 153 patients continued anti-EGFR mAb after secondary resection. These patients demonstrated a significant improvement in overall survival (OS) but not in time to treatment failure. Postresection anti-EGFR mAb conferred OS benefits compared to no anti-EGFR mAb (43.17 vs. 31.41 months; $P = 0.0064$). When stratified by assessment period, OS was longer in patients assessed between 2016 and 2018 than in those assessed between 2012 and 2015 (not reached vs. 39.87 months; $P = 0.1819$). However, no significant difference was observed in time to treatment failure when stratified by assessment period or primary tumor location. A multivariate analysis revealed that postresection anti-EGFR mAb was an independent predictor of prolonged OS. In conclusion, for mCRC patients who have undergone secondary resection after first-line anti-EGFR mAb plus doublet chemotherapy, continuing anti-EGFR mAb may significantly extend OS, regardless of the primary tumor location.

Keywords: Metastatic colorectal cancer, secondary surgery, epidermal growth factor receptor, monoclonal antibody, doublet chemotherapy

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide. In Taiwan, the annual numbers of new CRC cases and CRC deaths are approximately 15,000 and 5000, respectively [1, 2]. The incidence of CRC continues to increase in Taiwan. The primary treatment for early-stage CRC is surgery with or without adjuvant chemotherapy. However, approximately 25% of all patients with CRC develop metastasis at initial diagnosis, and approximately 50% of all patients with CRC develop metastasis, increasing the rate of CRC-related mortality [3]. The current medical interventions for metastatic CRC (mCRC) mainly comprise anti-vascular endothelial growth factor and anti-epidermal growth factor receptor (EGFR) mAb. Several drugs, such as bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib, have been approved for mCRC treatment [1, 4, 5]. The pan-Asian guidelines from the European Society for Medical Oncology recommend targeted therapy plus doublet chemotherapy as the standard first-line treatment for patients with mCRC. The presence of the *RAS* mutation should be tested in all patients during mCRC diagnosis [6]. Approximately 50% and < 5% of all patients with mCRC carry *RAS* and *BRAF* mutations, respectively; these patients do not respond to anti-EGFR mAb [7, 8]. The remaining 45% patients carry wild-type *RAS*; these patients, particularly those with left-sided tumors, receive anti-EGFR mAb plus doublet chemotherapy [9-12].

The liver is the predominant site for CRC metastasis. Approximately 30% of all patients with CRC with liver metastasis (CRLM) exhibit extended overall survival (OS) after liver surgery [13]. A cure rate of 16% has been observed in patients with CRLM, who became eligible for surgery after conversion chemotherapy [14]. In the LiverMetSurvey, patients receiving first-line systemic therapy exhibited the highest conversion rate, and the results indicate that the likelihood of cure is the highest after first-line conversion chemotherapy [15]. Among the two categories of targeted therapy, anti-EGFR mAb provides improved response rates and tumor shrinkage percentages [16]. Thus, anti-EGFR mAb plus chemotherapy is preferred when considering conversion surgery for patients with mCRC [3, 9].

To the best of our knowledge, no standard guideline is available for determining whether patients with CRLM should continue targeted therapy after liver surgery [17]. The National Comprehensive Cancer Network recommends only FOLFOX, without any targeting agents, for patients with initially resectable CRLM. Few studies involving patients undergoing conversion surgery have evaluated the efficacy of incorporating targeted therapy into the postoperative treatment regimen [18-20]. In several prospective controlled trials, if patients with CRLM were not selected for conversion surgery, they received postoperative therapy. Some post hoc studies have not defined the duration of postmetastasectomy treatment [21, 22]. Although the phase III New EPOC trial evaluated the efficacy of combining anti-EGFR mAb with perioperative chemotherapy, this trial focused on patients with initially resectable CRLM [22].

We previously examined chemotherapy regimens after primary resection [17]. In the present study, we analyzed the benefits of postoperative anti-EGFR mAb for obtaining valuable insights for clinical practice.

Methods

Data source

This was a retrospective, nationwide, population-based, cohort study. Relevant data were collected by linking three nationwide databases: the National Health Insurance Research Database (inpatient and outpatient prescriptions), Taiwan Cancer Registry (patient demographics and disease status), and National Death Registry (death records). Data were retrieved from the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. The process of data retrieval and the applicability of these databases to our research have been described previously [17, 23, 24]. Patients' personal data in these nationwide databases were deidentified, ensuring data anonymity. Results applying to < 3% of the target group were not processed to ensure privacy. The study was approved by the Institutional Review Board of National Taiwan University Hospital (Approval number: NTUH-REC No.: 202206062W). Written informed consent was waived due to the retrospective nature of the study.

Study population and variables

The inclusion criteria were as follows: receiving a histologically confirmed diagnosis of primary CRC (ICD-O-3: C180-C189, C19, and C20); receiving a diagnosis of wild-type *KRAS* mCRC; being aged ≥ 18 years; receiving first-line systemic therapy with either cetuximab or panitumumab between January 1, 2013, and December 31, 2019; receiving targeted therapy in combination with either irinotecan or oxaliplatin; and undergoing secondary resection or radiofrequency ablation for liver metastasis during the study period and receiving at least two cycles of chemotherapy. The exclusion criteria were as follows: unavailability of clinical data, diagnosis of hematological malignancies or Kaposi sarcoma (ICD-O-3 morphology code: 9140 and 9590-9989), simultaneous use of irinotecan and oxaliplatin or nonuse of either irinotecan or oxaliplatin, and postoperative alteration of the backbone of chemotherapy (from irinotecan to oxaliplatin or vice versa) and preoperative use of any targeting agent. Patients were divided into postoperative chemotherapy-only group and postoperative anti-EGFR mAb plus chemotherapy groups on the basis of their status after secondary surgery. Left-sided CRC was defined as primary tumors originating in the rectum, sigmoid colon, descending colon, or splenic flexure, whereas right-sided CRC was defined as primary tumors originating in the cecum, ascending colon, hepatic flexure, or transverse colon. Individuals aged ≥ 70 years were regarded as older patients.

Statistical analysis

The index date was the date when the first dose of anti-EGFR mAb plus chemotherapy was administered. OS was calculated as the interval from the index date to the date of death; data were censored if patients survived beyond the latest date of follow-up (December 31, 2019). Time to treatment failure (TTF) was calculated as the interval from the index date to that of the first dose of the subsequent line of chemotherapy. Because re-introduction strategy was usually favored when recurrence or progressive diseases were observed for patients who were very sensitive to first-line treatment, we choose TTF as our surrogate endpoint rather than other traditional endpoints, such as treatment duration or progression-free survival. Continuous variables were compared using the independent *t* or Wilcoxon rank-sum test and are presented in terms of mean ± standard deviation values. Categorical variables were compared using the chi-square or Fisher exact test and are presented in terms of frequency and percentage values. OS and TTF were estimated using the Kaplan-Meier method. Between-group differences were determined using a log-rank test. To identify potential predictors of OS and TTF, we would apply univariate Cox proportional-hazards model first. To eliminate possible confounding factors and any interactions among factors, we would also apply multivariate Cox proportional-hazards model subsequently. A two-sided *P* value of < 0.05 indicated statistical significance. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Results

Patient demographics

This study included 174 patients. The CONSORT diagram is presented in **Figure 1**. A total of 154 patients (87.9%) continued anti-EGFR mAb plus chemotherapy after secondary surgery, whereas 21 (12.1%) received only chemotherapy (**Table 1**). The median follow-up duration was 36.5 months in the postoperative anti-EGFR mAb group and 29.3 months in the chemotherapy-only group. No significant between-group difference was observed in the following baseline characteristics: age, sex, primary tumor location, initial tumor stage, hospital area, and hospital level. The treatment duration was longer in the chemotherapy-only group than in the postoperative anti-EGFR mAb group (17.1 vs. 10.1 months; $P < 0.0001$). The death rate was lower in the post-operative anti-EGFR mAb group (52.3% vs. 81.0%; P = 0.0064).

Treatment outcomes

The median OS was longer in the postoperative anti-EGFR mAb group than in the chemotherapy-only group (median values: 43.17 vs. 31.41 months; $P = 0.0064$; **Figure 2A**). Notably, when patients were stratified by primary tumor location, no significant between-group difference was observed in median OS (left vs. unknown vs. right: 40.31 vs. 38.79 vs. 42.35 months; **Figure 2B**). Patients were further stratified into

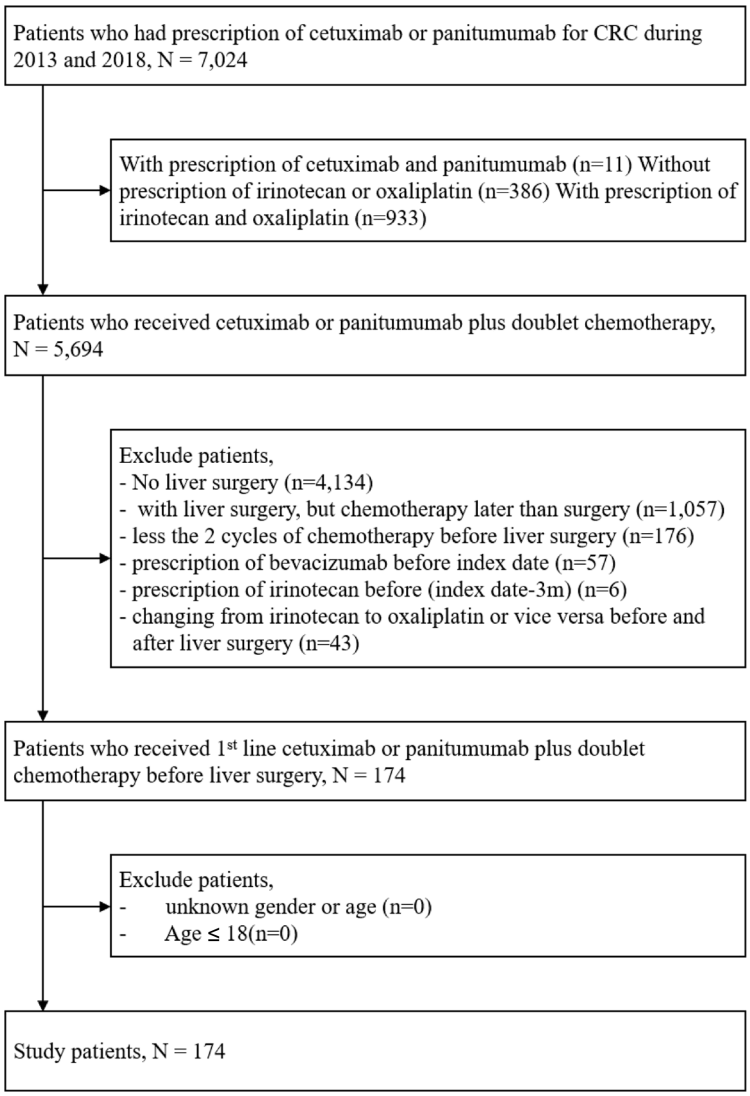

Figure 1. CONSORT diagram for this study according to inclusion and exclusion criteria.

two groups by assessment period: patients assessed between 2012 and 2015 and those assessed between 2016 and 2018. OS was longer in patients assessed during 2016-2018 than in those assessed during 2012-2015 (median values: not reached vs. 39.87 months; *P* = 0.1819; **Figure 2C**).

As shown in **Figure 3A**, TTF did not differ significantly between the postoperative anti-EGFR mAb and chemotherapy-only groups (median values: 21.85 vs. 26.18 months; P = 0.679). The findings suggest that continuous anti-EGFR mAb therapy in the context of chemotherapy after secondary resection does not increase the likelihood of treatment discontinuation. The analysis of TTF was further stratified by primary tumor location and assessment period to explore potential variations in treatment failure duration across these subgroups and to understand if specific characteristics influence the effectiveness of continuous anti-EGFR mAb therapy alongside chemotherapy. As shown in **Figure 3B**, no significant difference in median TTF was observed among patients stratified by primary tumor location, with median values of 22.89 months for left-sided, 18.20 months for unknown, and 44.58 months for right-sided tumors (P = 0.169). Furthermore, while TTF appeared to be longer in patients assessed during the period of 2016-2018 compared to those assessed during 2012-2015 (median values: 30.55 vs. 19.45 months; **Figure 3C**), the difference did not reach statistical significance (P = 0.129).

Results of the multivariate analysis

Given the significant survival benefits observed with continuous anti-EGFR mAb therapy in patients undergoing secondary resection, it is critical to further evaluate the impact of various clinical factors on OS. The Cox proportional-hazards analysis was performed to identify significant predictors for OS (**Table 2**). The univariate analysis showed that continuous anti-EGFR mAb therapy after secondary surgery (Hazard ratio [HR] = 0.49, 95% confidence interval [CI]: 0.29-0.83; P = 0.008) was associated with favorable OS, while a Charlson comorbidity index (CCI) score of ≥ 3 was significantly associated with worse OS (HR = 2.14, 95% CI: 1.11-4.12; P = 0.023). These two parameters remained significant in multivariate analysis (Hazard ratio [HR] = 0.44, P = 0.015; [HR] = 2.14, P = 0.041, respectively).

Table 1. Patient demographics

	Total (N = 174)	Anti-EGFR mAb + chemotherapy (N = 153)	Chemotherapy-only (N = 21)	*P* value
	n (%)	n (%)	n (%)	
Sex				
Male	106 (60.92)	92 (60.13)	14 (66.67)	0.57
Female	68 (39.08)	61 (39.87)	7 (33.33)	
Age				
Mean (SD)	57 (11.97)	57 (11.81)	61.18 (12.63)	0.09
Median	57	57	64.48	
Age				
< 60	100 (57.47)	91 (59.48)	9 (42.86)	0.15
60+	74 (42.53)	62 (40.52)	12 (57.14)	
Hospital area				
North	89 (51.15)	84 (54.9)	5 (23.81)	0.04
South	50 (28.74)	40 (26.14)	10 (47.62)	
Center or east	35 (20.11)	29 (18.95)	6 (28.57)	
Hospital level				
Medical Center	126 (72.41)	113 (73.86)	13 (61.9)	0.25
Others	48 (27.59)	40 (26.14)	8 (38.1)	
Primary site				
Left	92 (52.87)	81 (52.94)	11 (52.38)	0.40
Right	19 (10.92)	15 (9.8)	4 (19.05)	
Others	63 (36.21)	57 (37.25)	6 (28.57)	
Initial stage				
III-IV	164 (94.25)	143 (93.46)	21 (100.00)	0.61
Other	10 (5.75)	10 (6.54)	0 (0.00)	
Chemotherapy backbone				
Irinotecan + 5FU	161 (92.53)	143 (93.46)	18 (85.71)	0.20
Oxaliplatin + 5FU	13 (7.47)	10 (6.54)	3 (14.29)	
Follow-up time, months				
Mean (SD)	39 (17.68)	40 (17.83)	33.01 (15.74)	0.11
Median (Q1, Q3)	35 (26.03, 47.83)	36 (27.03, 48.67)	29.33 (23.93, 40.37)	
Treatment duration, months				
Mean (SD)	13.34 (8.25)	12.45 (7.47)	19.80 (10.72)	< 0.0001
Median (Q1, Q3)	10.38 (7.97, 15.07)	10.07 (7.80, 14.63)	17.13 (12.17, 25.97)	
Death events				
Yes	97 (55.75)	80 (52.29)	17 (80.95)	0.0064
No	77 (44.25)	73 (47.71)	4 (19.05)	

Next, univariate and multivariate analyses were performed to explore potential clinical factors that might impact TTF (**Table 3**). In univariate analysis, TTF was significantly associated with the level of the hospital where patients received treatment (HR = 0.63, 95% CI: 0.41-0.98; P = 0.041), suggesting that facility-related factors might play a role in treatment duration. However, after adjusting for multiple variables, the multivariate analysis indicated that no factor, including the type of hospital or primary tumor location, significantly impacted TTF in this patient population (all P > 0.05, **Table 3**). This finding suggests that treatment duration is unlikely to be adversely or favorably affected by these specific clinical characteristics, making continuous anti-EGFR mAb therapy potentially broadly applicable across patient types and treatment settings within this population.

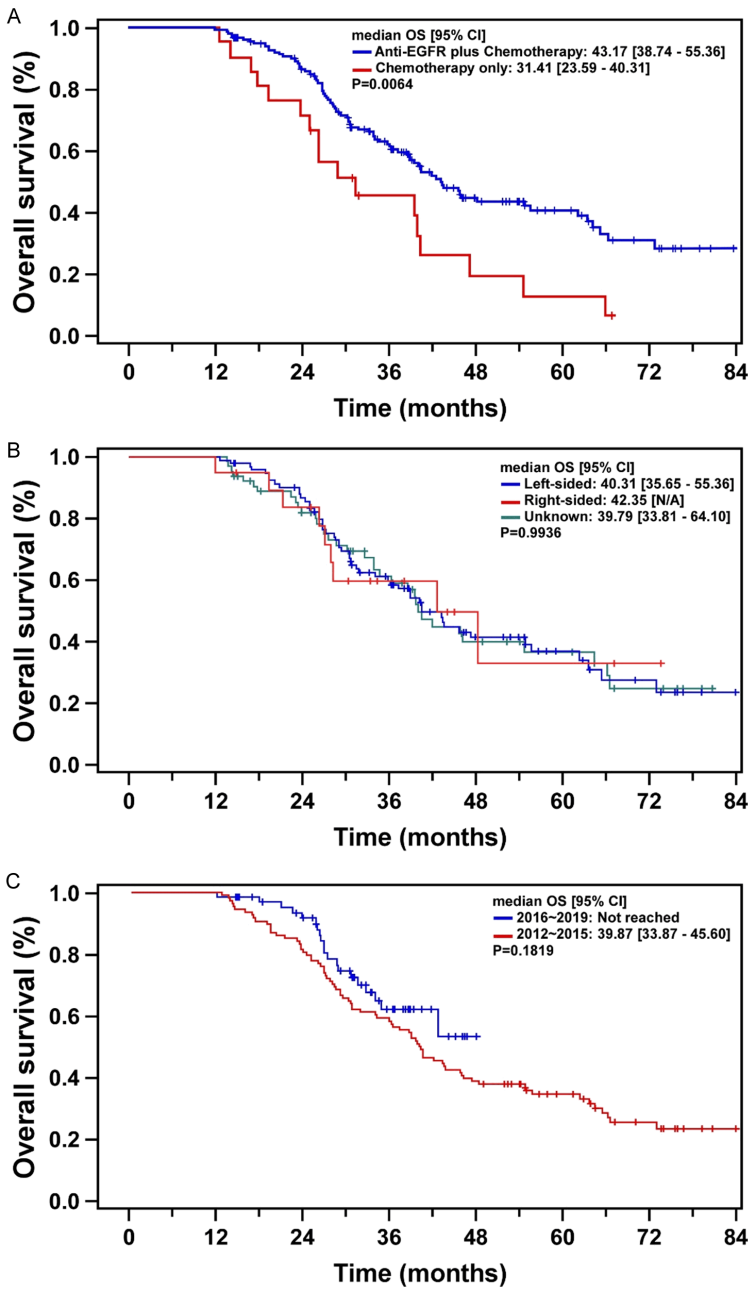

Figure 2. Kaplan-Meier plots of overall survival. Overall survival was compared (A) between patients who continued anti-EGFR therapy after conversion surgery and those who received chemotherapy-only, (B) among patients with right-sided primary tumors, those with left-sided primary tumors, and unknown primary tumor locations, and (C) between patients assessed during the 2016-2019 period and those assessed during the 2012-2015 period. Only continued anti-EGFR therapy arm had significantly impact on longer overall survival.

Discussion

Our study focused on patients with initially unresectable wild-type *KRAS* mCRC receiving first-line anti-EGFR mAb plus doublet chemotherapy and undergoing subsequent curative surgery after systemic conversion therapy. If patients maintained their first-line anti-EGFR mAb plus chemotherapy as adjuvant therapy after secondary surgery, they exhibited significantly better outcomes (OS) than did those receiving chemotherapy alone. To the best of our knowledge, the present study is the first to confirm that anti-EGFR mAb should be continued after curative surgery to improve OS in patients with mCRC.

Controversies still exist regarding the postoperative adjuvant therapy regimen. After the publication of the results of the EORTC 40983 study, some physicians recommended FOLFOX instead of adjuvant therapy [25]. However, the EORTC 40983 study focused on perioperative therapy, specifically targeting patients with initially resectable tumors. Conversely, our study focused on patients with initially unresectable tumors, which became resectable after neoadjuvant anti-EGFR mAb plus doublet chemotherapy. We excluded 68 patients who transitioned to FOLFOX after conversion surgery and thus focused on patients who maintained their original chemotherapy backbone, aligning closely with studies designed for patients undergoing conversion surgery for liver metastasis [18, 19]. The reason for regimen changes may be attributable to poor response to the previous first-line regimen.

The decision to continue mAb, particularly anti-EGFR mAb, plus chemotherapy after curative surgery remains contentious. Few randomized, prospective phase III clinical trials have addressed this specific topic. In the NEW EPOC

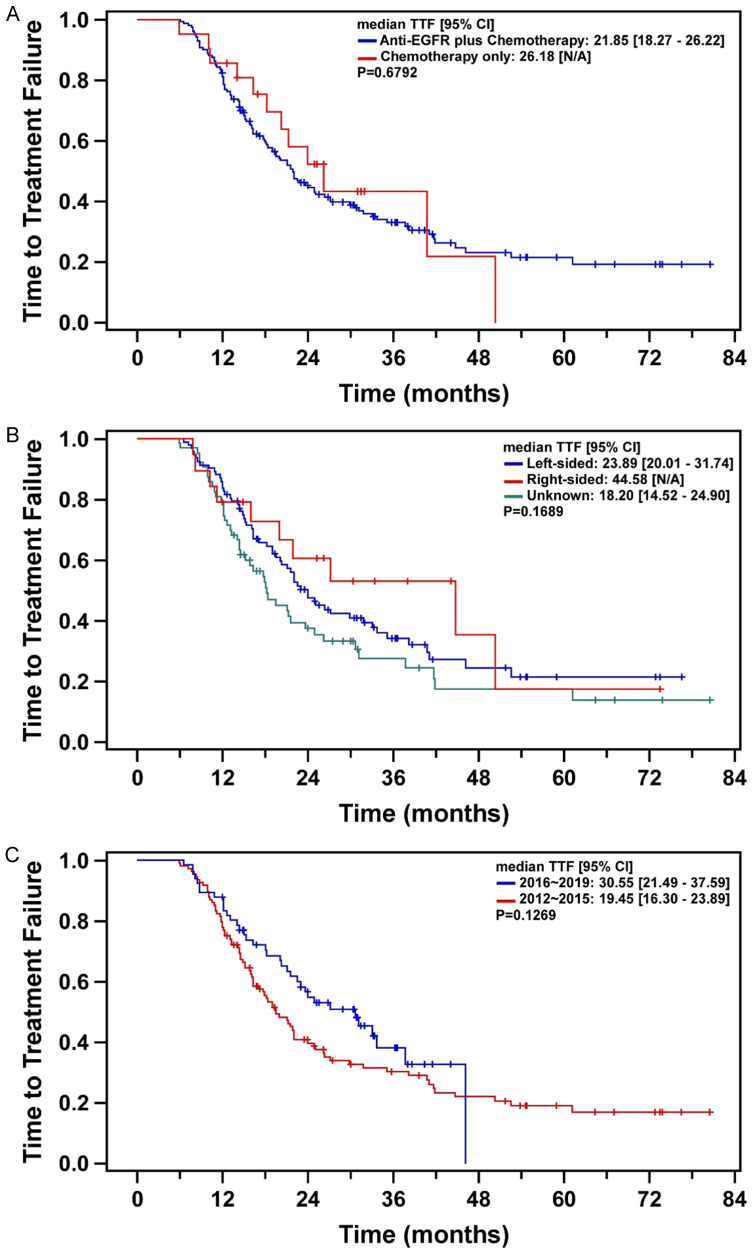

Figure 3. Kaplan-Meier plots of time to treatment failure. Time to treatment failure was compared (A) between patients who continued anti-EGFR therapy after conversion surgery and those who received chemotherapy-only, (B) among patients with right-sided primary tumors, those with left-sided primary tumors, and unknown primary tumor locations, and (C) between patients assessed during the 2016-2019 period and those assessed during the 2012-2015 period. Although some trends were observed, none factor had significantly impact on time to treatment failure.

study, perioperative cetuximab plus FOLFOX yielded inferior survival outcomes compared with those of FOLFOX alone [22]. Akin to the EORTC 40983 study, the NEW EPOC study targeted patients in the perioperative setting, rather than those with initially unresectable tumors. We previously established that patients with initially resectable stage 4 mCRC represent a distinct population, markedly differing from those with initially unresectable mCRC [17]. Therefore, evidence from perioperative settings cannot be extrapolated to patients undergoing conversion surgery.

We found that continuing anti-EGFR mAb plus chemotherapy after secondary surgery improved OS, rather than TTF, compared with the outcomes of chemotherapy alone. The reason why the OS benefits did not translate into TTF benefits is difficult to explain. The Kaplan-Meier plot for OS revealed a subset of patients with prolonged OS in the postoperative anti-EGFR mAb group. The survival long-tail, observed in approximately 20% of patients, was evident in Kaplan-Meier plots for both OS and TTF. However, no such long-term survivors were present in the chemotherapy-only group. Our study underscores that for patients exhibiting initial favorable responses to anti-EGFR mAb plus chemotherapy, anti-EGFR mAb should be continued after curative surgery to improve the cure rate and ensure long-term survival. Modest et al. ever published a prospective phase II trial to address the importance of keeping anti-EGFR after conversion surgery. However, the result was negative, but the survival plot showed a benefit trend in both PFS and OS. This result is similar to our data, but our data provided a positive survival benefit [26].

In our study, we observed a significant disparity between treatment durations and overall survival in the two study groups: the chemothera-

Table 2. Results of the Cox proportional-hazards analysis for overall survival

Variables	N	Death	%	Univariate			Multivariate		
				HR	95% CI	*p*-value	HR	95% CI	*P* value
Group									
Chemotherapy-only	21	17	(80.95)	1			1		
Anti-EGFR mAb + chemotherapy	153	80	(52.29)	0.49	(0.29, 0.83)	0.008[a]	0.44	(0.23, 0.85)	0.015[a]
Group									
Irinotecan	161	93	(57.76)	1			1		
Oxaliplatin	13	4	(30.77)	0.88	(0.32, 2.42)	0.806	0.94	(0.31, 2.82)	0.915
Treatment age									
Age < 60	100	52	(52.00)	1			1		
Age ≥ 60	74	45	(60.81)	1.39	(0.93, 2.07)	0.108	1.02	(0.64, 1.61)	0.946
Sex									
Female	68	38	(55.88)	1			1		
Male	106	59	(55.66)	1.06	(0.71, 1.60)	0.769	0.97	(0.61, 1.54)	0.897
CCI									
0	95	55	(57.89)	1			1		
1-2	63	31	(49.21)	0.81	(0.52, 1.26)	0.357	1.10	(0.68, 1.77)	0.707
3~	16	11	(68.75)	2.14	(1.11, 4.12)	0.023[a]	2.14	(1.03, 4.43)	0.041[a]
Primary site									
Left	92	53	(57.61)	1			1		
Right	19	9	(47.37)	0.97	(0.48, 1.97)	0.931	0.89	(0.42, 1.90)	0.771
Others	63	35	(55.56)	1.01	(0.66, 1.55)	0.962	0.87	(0.53, 1.43)	0.581
Hosp level									
Medical center	126	67	(53.17)	1			1		
Others	48	30	(62.50)	0.93	(0.61, 1.44)	0.754	1.31	(0.70, 2.46)	0.400
Hosp area									
North	89	53	(59.55)	1			1		
South	50	26	(52.00)	0.84	(0.53, 1.35)	0.470	0.71	(0.30, 1.68)	0.433
Center or east	35	18	(51.43)	1.21	(0.71, 2.08)	0.489	0.76	(0.45, 1.30)	0.323
TTF year									
2012-2015	108	77	(71.30)	1			1		
2016-2018	66	20	(30.30)	0.71	(0.43, 1.18)	0.184	0.87	(0.50, 1.53)	0.633

CI, confidence interval; HR, hazard ratio. [a]$P < 0.05$. Right-sided colon: cecum, ascending colon, hepatic flexure, and transverse colon. Left-sided colon: splenic flexure, descending colon, sigmoid colon, and R-S junction.

py-only group had a significantly longer treatment duration (mean of 17.1 months) but shorter overall survival compared to the group receiving continuing anti-EGFR therapy plus chemotherapy (mean of 10.1 months). The longer treatment duration totally did not translate into longer survival benefits. Although this result might imply the strong benefit from longer anti-EGFR mAb exposure, there were many clinical factors that needed to be dig-out, such as cumulative toxicity or the diminishing returns associated with extended exposure to chemotherapy agents. Our study was mainly established by databases analysis and thus our study did possess many limitations which we will mention later in this manuscript. Since we cannot clarify the real causes of linger treatment durations, such as less R0 resections or less depth of responses, we only demonstrated this result and we tended to elaborate this result more conservatively.

Our study has some limitations. First, the sample size was relatively small. The data were extracted from a nationwide cohort. We applied stringent inclusion and exclusion criteria to

Table 3. Results of the Cox proportional-hazards analysis for time to treatment failure

Variables	N	TTF	%	Univariate			Multivariate		
				HR	95% CI	*p*-value	HR	95% CI	*P* value
Group									
Chemotherapy-only	21	12	(57.14)	1			1		
Anti-EGFR mAb + chemotherapy	153	103	(67.32)	1.14	(0.62, 2.07)	0.678	1.23	(0.64, 2.40)	0.536
Group									
Irinotecan	161	112	(69.57)	1			1		
Oxaliplatin	13	3	(23.08)	0.32	(0.10, 1.00)	0.051	0.41	(0.12, 1.42)	0.159
Treatment age									
Age < 60	100	70	(70.00)	1			1		
Age ≥ 60	74	45	(60.81)	0.98	(0.67, 1.43)	0.917	1.07	(0.70, 1.65)	0.759
Sex									
Female	68	45	(66.18)	1			1		
Male	106	70	(66.04)	1.07	(0.73, 1.55)	0.737	1.01	(0.66, 1.55)	0.959
CCI									
0	95	66	(69.47)	1			1		
1-2	63	39	(61.90)	0.80	(0.54, 1.19)	0.265	0.82	(0.54, 1.23)	0.333
3~	16	10	(62.50)	1.36	(0.70, 2.67)	0.364	1.79	(0.85, 3.76)	0.125
Primary site									
Left	92	60	(65.22)	1			1		
Right	19	10	(52.63)	0.76	(0.39, 1.49)	0.430	0.85	(0.42, 1.72)	0.644
Others	63	45	(71.43)	1.33	(0.90, 1.97)	0.147	1.37	(0.91, 2.06)	0.135
Hosp level									
Medical center	126	84	(66.67)	1			1		
Others	48	31	(64.58)	0.72	(0.48, 1.09)	0.119	0.63	(0.41, 0.98)	0.041[a]
Hosp area									
North	89	64	(71.91)	1			1		
South	50	36	(72.00)	0.93	(0.62, 1.40)	0.717	0.87	(0.56, 1.37)	0.552
Center or east	35	15	(42.86)	0.57	(0.32, 1.00)	0.050	0.59	(0.32, 1.09)	0.092

CI, confidence interval; HR, hazard ratio. [a]$P < 0.05$. Right-sided colon: cecum, ascending colon, hepatic flexure, and transverse colon. Left-sided colon: splenic flexure, descending colon, sigmoid colon, and R-S junction.

eliminate the effects of potential confounders, such as delayed postoperative chemotherapy or altered chemotherapy regimens. This allowed for a clear comparison between postoperative anti-EGFR mAb and non-EGFR mAb without any bias. However, we could analyze only TTF and not disease-free survival. Data were collected by linking three national databases in Taiwan. For privacy protection, all data were anonymized. Therefore, not all personal information, such as computed tomography scans, was available for analysis. Although we could not shed light on disease-free survival, the data on TTF indicate the timing of recurrent disease or failure of first-line treatment even after re-introduction and can thus serve as a good alternative marker of disease-free survival.

Second, we could not clarify whether patients underwent R0/R1 or R2 resection during conversion surgery. In Taiwan, permission from the National Health Insurance Bureau is required for anti-EGFR mAb for mCRC: physicians must apply to the bureau to obtain an approval letter for prescribing anti-EGFR mAb to their patients. The first approval letter is for nine courses of anti-EGFR mAb. Physicians must apply for a second approval letter if patients are in complete response, partial response, or stable disease after the first 18 weeks of treatment. Thus, patients undergoing R2 resection might have applied for anti-EGFR mAb for the treatment of measurable lesions remaining after resection; this might have led to their inclusion in the postoperative anti-EGFR therapy group.

Patients with R0 resection were likely included in the chemotherapy-only group. Evidence suggests improved survival outcomes for these patients [27]. However, we found that OS was relatively long in patients who continued anti-EGFR mAb after secondary surgery. Therefore, most patients in our groups might have undergone R0 resection.

Finally, our study was retrospective. Nonetheless, it still provides a strong rationale for prospective clinical trials.

Conclusion

Our findings suggest that in patients with initially unresectable mCRC who are responsive to first-line anti-EGFR mAb plus doublet chemotherapy and subsequently undergo curative surgery, postoperative maintenance of anti-EGFR mAb plus chemotherapy can improve OS and the likelihood of cure compared with the outcomes of chemotherapy alone. This study offers a rationale for determining an appropriate postoperative treatment regimen and highlights the need for relevant prospective clinical trials.

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Disclosure of conflict of interest

None.

Abbreviations

EGFR, Epidermal Growth Factor Receptor; mAb, Monoclonal Antibodies; mCRC, Metastatic Colorectal Cancer; OS, Overall Survival; CRC, Colorectal Cancer; CRLM, CRC with Liver Metastasis; TTF, Time to Treatment Failure.

Address correspondence to: Dr. Yi-Hsin Liang, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan. Tel: +886-223123456 Ext. 266007; Fax: +886-223711174; E-mail: liangyihsin@ntuh.gov.tw

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