Carcinoembryonic Antigen Half-life Is an Early Predictor of Therapeutic Effects in Induction Chemotherapy for Liver Metastases from Colorectal Cancer

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Abstract. *Aim: We evaluated the relationship between carcinoembryonic antigen half-life (CEA-HL) in the early period of induction chemotherapy for patients with liver metastases from colorectal cancer (CRLM) and their clinicopathological response. Patients and Methods: Seventy-four patients with initially unresectable CRLM received FOLFOX with or without bevacizumab and 30 patients underwent hepatic resection. The CEA-HL in the early postoperative period was investigated, and the pathological response was classified according to tumor regression grade (TRG). Results: The CEA-HL after the third chemotherapeutic course (CEA-HL3) was significantly shorter in responders compared to non-responders. In the 30 patients who underwent hepatectomy, the CEA-HL3 was significantly shorter in the major or complete-pathological-response group for the TRGs than in the the partial-pathological-response group. If the patients were divided into two groups according to the median value of 20 days, progression-free survival and overall survival were significantly better in those with CEA-HL3 below the cut-off. Conclusion: The CEA-HL is an early predictor of the pathological response and prognosis after induction chemotherapy for CRLM.*

Liver metastases occur in approximately 30% of all patients with colorectal cancer (CRC), and account for at least two-thirds of deaths of these patients (1). Furthermore, approximately 60% to 70% of patients show recurrence after hepatic resection for liver metastases from CRC (CRLM) (2). Combination chemotherapy including fluorouracil with irinotecan or oxaliplatin improves the survival of patients with CRLM (3-5). Oxaliplatin-based chemotherapy, including the leucovorin-fluorouracil-oxaliplatin (FOLFOX) regimen, can lead to tumor down-staging in some patients with initially unresectable CRLM, and improve their survival (6-10). Early prediction of tumor response is a quite important issue because the treatment strategy will be promptly decided (11, 12).

Carcinoembryonic antigen (CEA) was first identified in 1965 (13), and has been widely used as a biomarker of several types of digestive cancers. It is a good prognostic marker of CRC: the postoperative CEA level can predict the success of curative resection, and CEA is the biomarker of choice for monitoring the response to systemic therapy for metastatic CRC (2, 4, 14, 15). It is also a useful biomarker for reflecting the response to chemotherapy for CRLM, and in several studies, its kinetics during chemotherapy have been investigated in relation to various clinicopathological parameters (16-18). However, the literature includes only a few detailed reports on the kinetics of CEA during induction chemotherapy for CRLM and its relationship with the pathological response. In the present study, we aimed to evaluate the relationship between the half-life of serum CEA (CEA-HL) and the pathological response and long-term outcome in the early period of induction chemotherapy for CRLM.

Patients and Methods

From May 2005 to December 2009, 105 patients with initially unresectable CRLM or extra-hepatic metastases received induction chemotherapy, and 88 of these patients were treated with more than three courses of FOLFOX with/without bevacizumab as the first-line therapy.

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Nine patients with insufficient data and five in whom CEA was in normal range before induction chemotherapy were excluded from the analyses. Finally, 74 patients were enrolled in this study and 30 patients became eligible for hepatic resection after induction chemotherapy. They had histologically proven colorectal adenocarcinoma with liver metastases, and no history of other carcinoma in the previous five years. Written informed consent was obtained from all patients, and this study conformed to the tenets of the World Medical Association's Declaration of Helsinki and was approved by the local Review Committee.

Chemotherapeutic regimen. FOLFOX was administered mainly as outpatient chemotherapy on the basis of the modified FOLFOX6 protocol as follows: a 2-h infusion of leucovorin (200 mg/m^2) and oxaliplatin (85 mg/m^2) followed by a fluorouracil bolus (400 mg/m^2) and a 46-h continuous infusion of fluorouracil (2400 mg/m^2) for two days every two weeks. Bevacizumab (5 mg/kg) was administered on day 1 of the biweekly regimen. The treatment was continued until diagnosis of resectable CRLM, disease progression or unacceptable toxicity occurred, or the patient decided to discontinue treatment. After hepatic resection, FOLFOX was basically continued for up to 12 cycles of preoperative and postoperative chemotherapy in total.

Clinical response evaluation. The clinical analysis was based on medical imaging and patient records in the Kumamoto University CRLM database after each cycle. Before chemotherapy, abdominal ultrasonography, and computed tomography (CT) or magnetic resonance imaging (MRI) were performed according to the identified targets. CT scans were repeated after every two or three chemotherapeutic courses. The clinical response was defined according to the Response Evaluation Criteria in Solid Tumors Group guidelines during the CT scan evaluation (19).

Pathological response evaluation. The pathological response to chemotherapy was classified according to a modified version of Mandard's classification (20, 21). In this classification, five tumor regression grades (TRGs) are defined on the basis of the presence of residual tumor cells and the extent of fibrosis (21) as follows: TRG1, no residual tumor cells and abundant fibrosis; TRG2, a few residual tumor cells scattered throughout abundant fibrosis; TRG3, some residual tumor cells throughout predominant fibrosis; TRG4, predominant tumor cells throughout some fibrosis; and TRG5, abundant tumor cells and no fibrosis. For the pathological analysis, tumor samples were fixed in formalin for more than 24 h, embedded in paraffin, sectioned into slices of 5-10 mm in thickness, and stained with hematoxylin and eosin. The slides were examined independently by two pathologists. In patients with multiple metastases with different TRGs, the higher TRG was used as reference.

Measurement of CEA levels and CEA-HL. The serum CEA level was measured in all patients before each chemotherapeutic cycle, and 2.0 ng/ml was considered as the lower cut-off. The CEA kinetics during chemotherapy differed among the patients. The CEA-HL slope was determined by using a semilogarithmic plot of the serum CEA level measured at different time points. To assess the slope objectively, the CEA level before chemotherapy (baseline) and that after the first, second, and third chemotherapeutic courses were considered. The CEA-HL during the early period of chemotherapy was then determined using the Kohn equation (22), as follows: CEA-HL (days)=$0.3\times\Delta T/\ln$(CEA level at baseline/CEA level after each chemotherapeutic course) where ΔT is the time interval between the baseline and the each chemotherapeutic course. In the patients with static or increasing CEA levels, the CEA-HL was set at 100 days according to a previous study (23).

Table I. *Characteristics of the 30 patients who underwent hepatic resection after chemotherapy.*

Characteristic	No.	%
Tumor location		
Colonic	20	66.7
Rectal	10	33.3
Timing of liver metastasis		
Synchronous	22	73.3
Metachronous	8	26.7
Extra-hepatic metastases		
Negative	25	83.3
Positive	5	16.7
Chemotherapy regimen		
FOLFOX	22	73.3
FOLFOX+BV	8	26.7
Total chemotherapy cycles, n		
Mean	7.8	-
Range	3-19	-
Hepatectomy		
Major	13	43.3
Minor	17	56.7
TRG		
1	1	3.3
2	5	16.7
3	8	26.7
4	7	23.3
5	9	30
Relapse site after hepatectomy		
None	12	40
Remnant liver	11	35.5
Lung	6	19.4
Lymph node	4	12.9
Bone	3	9.7

FOLFOX, Folinic acid, 5-fluorouracil, and oxaliplatin; BV, bevacizumab; TRG, tumor regression grade.

Statistical analysis. We used box plots and Student's *t*-test to analyze the relationship between the CEA-HL and the clinicopathological response after each chemotherapeutic course. Categorical variables were compared by using the chi-square test. Progression-free and overall survival was calculated from the date of the first chemotherapy. Univariate survival analyses were performed using the Kaplan–Meier method and log-rank tests. For all the statistical tests, the level of significance was defined as $p<0.05$. All statistical analyses were performed with the StatView5.0 software program (SAS Institute, Inc., Cary, NC, USA).

Results

Patients' characteristics. All the patients had a World Health Organization performance status of 0 to 2, 70.2% (52/74) of the patients were of male gender, and the median age was 65

Table II. *Correlation between clinical parameters and pathological response.*

	Category	n	Pathological response			
			TRG1-2	TRG3	TRG4-5	*p*-Value
No. of liver metastases	<3	16	3	5	8	
	≥3	14	3	3	8	0.83
Largest tumor diameter	<5.0 cm	20	3	6	11	
	≥5.0 cm	10	3	2	5	0.60
Clinical response	SD	10	1	3	6	
	PR	20	5	5	10	0.63
Pre-chemotherapy CEA	<24 ng/ml	15	2	3	10	
	≥24 ng/ml	15	4	5	6	0.34
CEA-HL3	<20 days	15	6	3	6	
	≥20 days	15	0	5	10	0.02

Cut-off values for pre-chemotherapy CEA and CEA-HL3 were median values. *TRG*, tumor regression grade; *SD*, stable disease after third chemotherapeutic course; *PR*, partial response after third chemotherapeutic course; CEA-HL3, carcinoembryonic antigen half-life after third chemotherapeutic course.

years (range=34-83 years). Furthermore, the majority of patients (54/74; 73%) had synchronous liver metastases. Moreover, the majority (57/74; 77%) received FOLFOX alone. The clinical response after the first three chemotherapeutic courses was as follows: progressive disease (PD) in 17.6% (13/74); stable disease (SD) in 39.2% (29/74); and partial response (PR) in 43.2% (32/74).

Table I shows the clinicopathological characteristics of the 30 (40.5%) patients who underwent hepatic resection after chemotherapy (mean=7.8 courses). The median follow-up time after hepatic resection was 24 months (range=3-48 months). During this period, 18 (60%) patients experienced recurrence and nine (30%) patients died.

CEA kinetics during the early period of chemotherapy. The CEA kinetics in the first three courses of induction chemotherapy was investigated in the 74 patients (Figure 1). The serum CEA level gradually increased in the PD group, but decreased in the SD and PR groups. The level after the third chemotherapeutic course was significantly higher in the PD compared to the SD or PR groups (636.9±514.9 *vs*. 126.5±46.6 ng/ml, $p=0.04$) (Figure 1a). Furthermore, the serum CEA level gradually decreased in the patients with PR, and a significant difference was noted between the baseline level and that after the third chemotherapeutic course (622.2±206 *vs*. 111.8±38.2 ng/ml, $p=0.02$) (Figure 1b).

The CEA-HL after the second chemotherapeutic course (CEA-HL2) was significantly shorter in the PR group compared to the SD ($p=0.01$) and PD ($p<0.01$) groups. The CEA-HL after the third chemotherapeutic course (CEA-HL3) was also significantly shorter in the PR group than the SD ($p<0.01$) and PD ($p<0.01$) groups, and in the SD rather than the PD group ($p=0.04$) (Figure 1c). Moreover, the CEA-HL3 was significantly shorter in patients who underwent hepatic resection than in those for whom hepatic resection remained impossible ($p<0.01$) (Figure 1d).

Relationship between CEA-HL and pathological response. A relationship between the CEA-HL3 and the pathological response was demonstrated in the 30 patients who underwent resection (Figure 2). The response was classified into three groups on the basis of the TRGs according to a previous report (21): TRG1/2 (n=6), major or complete pathological response; TRG3 (n=8), partial pathological response; and TRG4/5 (n=16), no tumor regression or pathological response. The CEA-HL3 was significantly longer in the TRG3 group than in the TRG1/2 group ($p=0.01$). Table II demonstrates the relationships of the clinical parameters and CEA-HL3 with the TRG in these patients. Only the CEA-HL3 was significantly related to TRG ($p=0.02$).

Relationship between CEA-HL and survival. The relationships between the clinical parameters and survival were investigated in the 30 patients who underwent reaction (Table III). In the univariate analyses, the CEA-HL3 was significantly influenced the progression-free survival ($p=0.03$) and overall survival ($p=0.02$). The patients were divided into two groups according to the median CEA-HL3 value of 20 days. Figure 3 shows the survival curve of the patients according to CEA-HL3 value. Progression-free survival ($p=0.03$) and overall survival ($p=0.02$) were significantly better in those with CEA-HL3 below the cut-off.

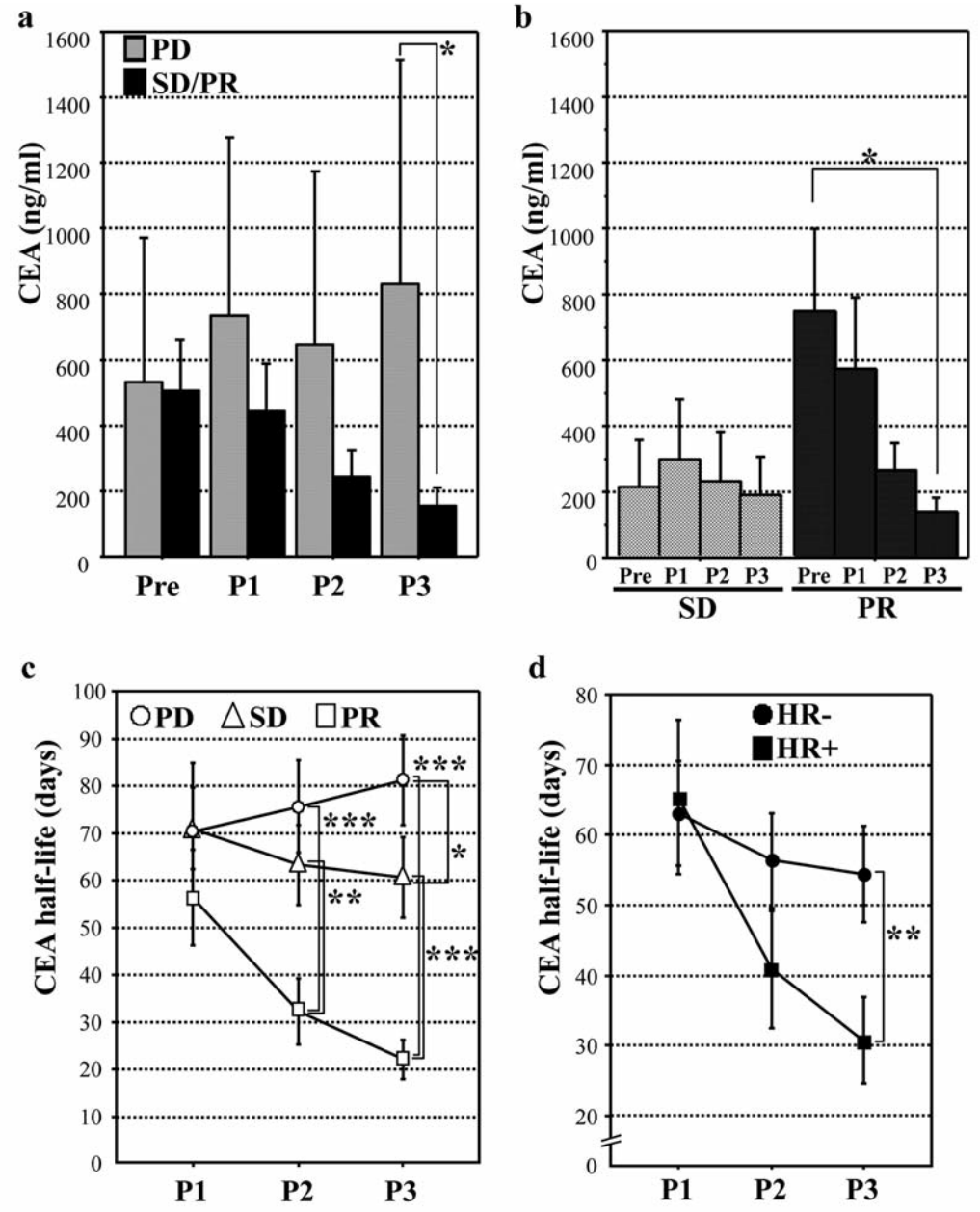

Figure 1. *Carcinoembryonic antigen (CEA) kinetics during the first three courses of induction chemotherapy in the 74 patients with colorectal liver metastases (CRLM). The changes in the serum CEA levels were compared between those with progressive disease (PD; n=13) and stable disease (SD) or partial response (PR; n=61) (a) and between those with SD (n=29) and with PR (n=32) (b). The changes in the CEA half-life (CEA-HL) were also compared among the PD, SD, and PR groups (c) and between the patients without hepatic resection (HR−; n=44) and those with (HR+; n=30) (d). *p<0.05, **p<0.01, ***p<0.001. Pre, baseline; P1, after first chemotherapeutic course; P2, after second chemotherapeutic course; P3, after third chemotherapeutic course.*

Discussion

The relationship between the early CEA kinetics and the clinicopathological response to induction chemotherapy in patients with CRLM, especially those treated by hepatic resection, has been seldom examined. We first analyzed the serum CEA levels and CEA-HL according to the early clinical response to induction chemotherapy. Both the absolute CEA level and the CEA-HL slope were the most significant prognostic factors after three courses of chemotherapy. In

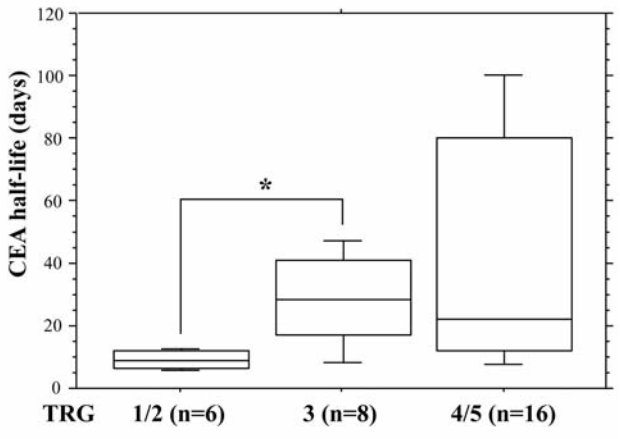

Figure 2. *Box plot analysis of the carcinoembryonic antigen half-life (CEA-HL) after third chemotherapeutic course and the relationship with the tumor regression grades (TRGs). *p<0.05. The central bar is a median value. Top and bottom of error bar and box is maximum and minimum, and 75th percentile and 25th percentile, respectively.*

Table III. *Correlation between clinical parameters and survival.*

	Category	n	Univariate analysis	
			MST (months)	*p*-Value
Progression-free survival				
No. of liver metastases	<3	16	9.2	
	≥3	14	5.2	0.19
Largest tumor diameter	<5.0 cm	20	6.6	
	≥5.0 cm	10	5.2	0.89
Clinical response	SD	10	3.3	
	PR	20	9.2	0.13
Pre-chemotherapy CEA	<24 ng/ml	15	9.2	
	≥24 ng/ml	15	4.7	0.37
CEA-HL3	<20 ng/ml	15	26.4	
	≥20 days	15	4.0	0.03
Overall survival				
No. of liver metastases	<3	16	NR	
	≥3	14	NR	0.80
Largest tumor diameter	<5.0 cm	20	27.1	
	≥5.0 cm	10	NR -	0.73
Clinical response	SD	10	19.3	
	PR	20	NR -	0.03
Pre-chemotherapy CEA	<24 ng/ml	15	NR -	
	≥24 ng/ml	15	NR -	0.67
CEA-HL3	<20 days	15	NR -	
	≥20 days	15	24.0	0.02

CEA-HL3, (CEA) half-life after the third chemotherapeutic course; MST, median survival time; SD, stable disease after third chemotherapeutic course; PR, partial response after third chemotherapeutic course. Cut-off values of pre-chemotherapy CEA, CEA-HL3 were median values; NR, not reached.

patients with CRLM who receive induction chemotherapy, eligibility for resection is an independent prognostic factor (9, 10). Accordingly, the CEA-HL3 was significantly lower in the patients finally treated with compared to those without hepatic resection. Therefore, we consider the CEA-HL3 to be an important predictor of CRLM resectability in the early period of induction chemotherapy.

The TRG system is a useful tool for evaluating the pathological response to neoadjuvant chemotherapy for CRLM (21). The pathological response to chemotherapy is also related to survival (21, 24, 25). In the present study, the CEA-HL significantly predicted the pathological response, whereas the clinical response was not significantly different by the clinical parameters analyzed. Because the clinical response during induction chemotherapy depends only on the change in tumor size, the clinical parameters may fail to represent the true response to chemotherapy, as indicated in recent reports (26, 27). Therefore, the CEA kinetics should be evaluated before further treatments in patients receiving induction chemotherapy for CRLM.

The relationship between early tumor marker kinetics based on half-life analysis and the response and survival after induction chemotherapy has been reported for other types of cancer: carbohydrate antigen 125 in ovarian cancer (23, 28), alpha-fetoprotein in germ cell tumors (29), and prostate-specific antigen in prostate cancer (30). These findings likely indicate that early kinetics of tumor markers reflect the sensitivity of tumors and cancer cell survival after chemotherapy. In many clinical studies of chemotherapy for CRLM, the response is evaluated after the first two or three chemotherapeutic courses. If the final response to chemotherapy can be predicted in the early period, then ineffective treatment can be avoided. Early tumor shrinkage at eight weeks and six weeks can predict long-term survival for patients with metastatic CRC treated with first-line chemotherapy plus cetuximab and for patients with chemorefractory metastatic CRC treated with cetuximab with or without irinotecan (11, 12). Recently, early tumor response by week-2 non-enhanced MRI was found to be predictive of clinical outcome in patients with metastatic CRC treated with cetuximab or panitumumab (31). However, these studies all required diagnostic imaging and demonstrated no information of pathological effects in the resected liver.

Our study has some limitations. Firstly, its retrospective design inherently introduces certain types of bias. In fact, a few cases were excluded because of insufficient data, and the study included a limited number of patients. Consequently the findings in some patients might be difficult to interpret statistically. For example, among the patients with a CEA-HL2 of less than 19 days, five out of six had TRG1/2, and among those with a CEA-HL2 of 19 days or more, 62.5%

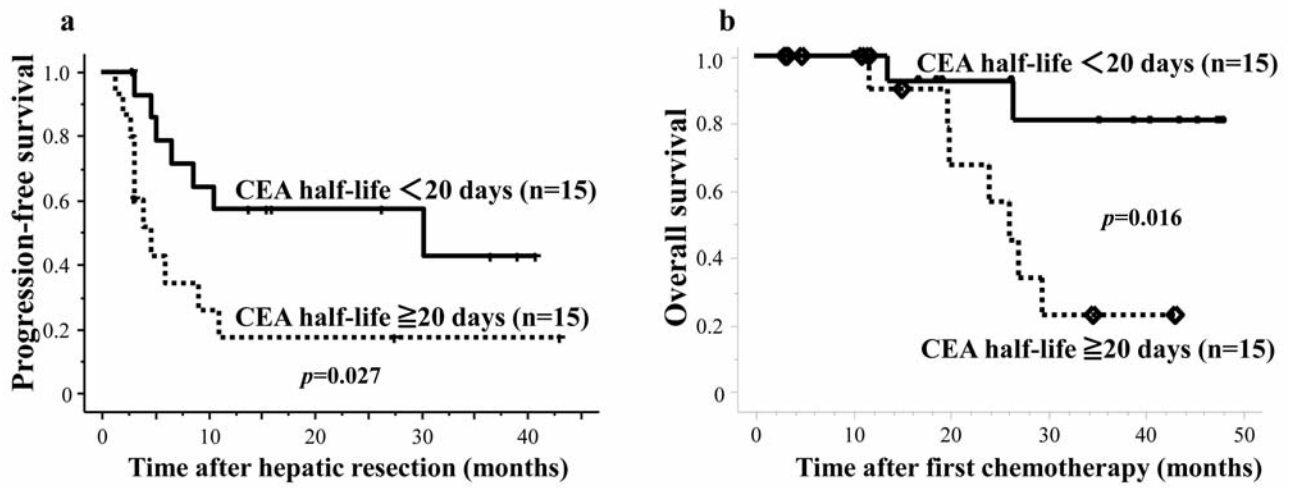

Figure 3. *The progression-free (a) and overall (b) survival of the 30 patients who underwent hepatic resection stratified by their carcinoembryonic antigen half-life (CEA-HL) after the third chemotherapeutic course.*

(10/16) had TRG4/5 (data not shown). Although these data after two chemotherapeutic courses were not significantly different, they tended to be associated with the pathological response. Because of a limited number of patients, further statistical analysis was difficult to perform, and differences were not demonstrated clearly.

In conclusion, the CEA-HL during the early period of induction chemotherapy can predict the pathological response and survival in patients with CRLM. It is easily measured and can contribute to proper decision making, avoiding ineffective treatment. A prospective multi-center study with a large patient population is warranted to confirm our results.

Conflicts of Interest

No conflicts of interest.

References

1 Kamangar F, Dores GM and Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol *24*: 2137-2150, 2006.

2 Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, Nitta H, Yoshidome H, Hatano E, Ueno M, Takamura H, Baba H, Kusuge T, Kokudo N, Takahashi K,Endoi, Wakabayashi G, Miyazaki M, Uemoto S, Ohta T, Kikuchi K, Takayama T, Yamaue H, Yamamoto M and Takada T: A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreatic Sci *19*: 72-84 2012.

3 Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM and McWilliams RR: Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol *27*: 3677-3683, 2009.

4 Rees M, Tekkis PP, Welsh FK, O'Rourke T and John TG: Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg *247*: 125-135, 2008.

5 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC and Alberts SR: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol *22*: 23-30, 2004.

6 Pozzo C, Basso M, Cassano A, Quirino M, Schinzari G, Trigila N, Vellone M, Giuliante F, Nuzzo G and Barone C: Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol *15*: 933-939, 2004.

7 Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F and Bismuth H: Rescue surgery for unresectable colorectal liver metastases down-staged by chemotherapy: a model to predict long-term survival. Ann Surg *240*: 644-658, 2004.

8 Leonard GD, Brenner B and Kemeny NE: Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol *23*: 2038-2048, 2005.

9 Beppu T, Hayashi N, Masuda T, Komori H, Horino K, Hayashi H, Okabe H, Baba Y, Kinoshita K, Akira C, Watanebe M, Takamori H and Baba H: FOLFOX enable high resectability and excellent prognosis for initially unresectable colorectal liver metastases. Anticancer Res *30*: 1015-1020, 2010.

10 Beppu T, Miyamoto Y, Sakamoto Y, Imai K, Nitta H, Hayashi H, Chikamoto A, Watanabe M, Ishiko T and Baba H: Chemotherapy

and targeted therapy for patients with initially unresectable colorectal liver metastases, focusing on conversion hepatectomy and long-term survival. Ann Surg Oncol *21(Suppl 3)*: 405-413, 2014.

11 Piessevaux H, Buyse M, De Roock W, Prenen H, Schlichting M, Van Cutsem E and Tejpar S: Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastatic colorectal cancer treated with cetuximab (BOND trial). Ann Oncol *20*: 1375-1382, 2009.

12 Piessevaux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S and Tejpar S: Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol *31*: 3764-3775, 2013.

13 Gold P and Freedman SO: Specific carcinoembryonic antigens of the human digestive system. J Exp Med *122*: 467-481, 1965.

14 Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, Somerfield MR, Hayes DF and Bast RC Jr.: ASCO. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol *24*: 5313-5327, 2006.

15 Fong Y, Fortner J, Sun RL, Brennan MF and Blumgart LH: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg *230*: 309-318, 1999.

16 Hanke B, Riedel C, Lampert S, Happich K, Martus P, Parsch H, Himmler B, Hohenberger W, Hahn EG and Wein A: CEA and CA 19-9 measurement as a monitoring parameter in metastatic colorectal cancer (CRC) under palliative first-line chemotherapy with weekly 24-hour infusion of high-dose 5-fluorouracil (5-FU) and folinic acid (FA). Ann Oncol *12*: 221-226, 2001.

17 Iwanicki-Caron I, Di Fiore F, Roque I, Astruc E, Stetiu M, Duclos A, Tougeron D, Saillard S, Thureau S, Benichou J, Paillot B, Basuyau JP and Michel P: Usefulness of the serum carcinoembryonic antigen kinetic for chemotherapy monitoring in patients with unresectable metastasis of colorectal cancer. J Clin Oncol *26*: 3681-3686, 2008.

18 Tsai HL, Chang YT, Chu KS, Chen CF, Yeh YS, Ma CJ, Wu DC, Kuo CH, Chan HM, Sheen MC and Wang JY: Carcinoembryonic antigen in monitoring of response to cetuximab plus FOLFIRI or FOLFOX-4 in patients with metastatic colorectal cancer. Int J Biol Markers *23*: 244-248, 2008.

19 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

20 Mandard AM1, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P and Samama G: Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer *73*: 2680-2686, 1994.

21 Rubbia-Brandt L1, Giostra E, Brezault C, Roth AD, Andres A, Audard V, Sartoretti P, Dousset B, Majno PE, Soubrane O, Chaussade S, Mentha G and Terris B: Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Ann Onco *2*: 299-304, 2007.

22 Kohn J: The dynamics of serum alpha-fetoprotein in the course of testicular teratoma. Scand J Immunol *8*: 103-107, 1978.

23 Gadducci A, Cosio S, Fanucchi A, Negri S, Cristofani R and Genazzani AR: The predictive and prognostic value of serum CA 125 half-life during paclitaxel/platinum-based chemotherapy in patients with advanced ovarian carcinoma. Gynecol Oncol *93*: 131-136, 2004.

24 Adam R, Wicherts DA, de Haas RJ, Aloia T, Lévi F, Paule B, Guettier C, Kunstlinger F, Delvart V, Azoulay D and Castaing D: Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol *26*: 1635-1641, 2008.

25 Klinger M, Tamandl D, Eipeldauer S, Hacker S, Herberger B, Kaczirek K, Dorfmeister M, Gruenberger B and Gruenberger T: Bevacizumab improves pathological response of colorectal cancer liver metastases treated with XELOX/FOLFOX. Ann Surg Oncol *17*: 2059-2065, 2010.

26 Neumann UP, Thelen A, Röcken C, Seehofer D, Bahra M, Riess H, Jonas S, Schmeding M, Pratschke J, Bova R and Neuhaus P: Nonresponse to pre-operative chemotherapy does not preclude long-term survival after liver resection in patients with colorectal liver metastases. Surgery *146*: 52-59, 2009.

27 Gallagher DJ, Zheng J, Capanu M, Haviland D, Paty P, Dematteo RP, D'Angelica M, Fong Y, Jarnagin WR, Allen PJ and Kemeny N: Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. Ann Surg Oncol *16*: 1844-1851, 2009.

28 Riedinger JM, Wafflart J, Ricolleau G, Eche N, Larbre H, Basuyau JP, Dalifard I, Hacene K and Pichon MF: CA 125 half-life and CA 125 nadir during induction chemotherapy are independent predictors of epithelial ovarian cancer outcome: results of a French multicentric study. Ann Oncol *17*: 1234-1238, 2006.

29 Gerl A, Lamerz R, Clemm C, Mann K, Hartenstein R and Wilmanns W: Does serum tumor marker half-life complement pretreatment risk stratification in metastatic nonseminomatous germ cell tumors? Clin Cancer Res *2*: 1565-1570, 1996.

30 Banu E, Banu A, Medioni J, Levy E, Thiounn N, Mejean A, Andrieu JM and Oudard S: Serum PSA half-life as a predictor of survival for hormone-refractory prostate cancer patients: modelization using a standardized set of response criteria. Prostate *67*: 1543-1549, 2007.

31 Ricotta R, Vanzulli A, Moroni M, Colnago B, Oriani M, Nichelatti M, Sarnataro C, Venturini F, Di Bella S, Maiolani M, Giganti MO, Sartore-Bianchi A and Siena S: Magnetic resonance imaging as an early indicator of clinical outcome in patients with metastatic colorectal carcinoma treated with cetuximab or panitumumab. Clin Colorectal Cancer *12*: 45-53, 2013.

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