Optimal use of current chemotherapy in multimodality therapy for advanced colorectal cancer

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Abstract. Treatment of advanced colorectal cancer (CRC) increasingly requires a multimodality approach, which adds to the complexity of clinical decision-making. This study investigates the optimal use of current chemotherapy in multimodality therapy for advanced CRC. We enrolled 208 patients with unresectable primary and metastatic (recurrent) CRC who underwent chemotherapy in our hospital. Radiofrequency ablation and/or secondary surgery were used depending on tumor response to chemotherapy. Disease sites varied among patients and included unresectable liver, lung and peritoneal metastasis. Chemotherapy produced cytoreduction in 71 of 208 patients (34%). Multimodality cytoreduction increased overall survival to a median of 46.0 months vs. 20.2 months with chemotherapy alone (P<0.0001). The response rate to chemotherapy was independently associated with cytoreduction. Molecular targeted therapy reduced the number of tumor cells sooner than conventional chemotherapy, and correlated with repeated cytoreduction that further prolonged survival. Aggressive chemotherapy as initial treatment for advanced CRC leads to cytoreduction and is associated with extended survival in patients receiving multimodality therapy.

Introduction

More than 1 million individuals worldwide develop colorectal cancer (CRC) every year (1). CRC is the second most common cause of mortality due to cancer (2), and is a major health problem in the Western world. Although surgery remains the mainstay treatment, the role of chemotherapy in CRC has expanded considerably over the past 10 years. Today, the majority of patients receive chemotherapy with 1 or more agents approved for treatment. Combination chemotherapy regimens consist of 5-fluorouracil (5-FU) and leucovorin (LV) with oxaliplatin or irinotecan. With the administration of molecular targeted agents (i.e., bevacizumab or cetuximab/panitumumab), therapy response rates of 50-80% have been achieved and median survival time (MST) has been prolonged to 20-24 months in metastatic CRC patients (3-7).

A number of treatment options are emerging from a growing database on combination therapy with these agents as well as new types of oral fluoropyrimidines (including capecitabine uracil/tegafur and S-1). The availability of multiple effective agents has also added complexity to decisions on optimal chemotherapy for patients with advanced CRC.

Resection of CRC liver or lung metastasis is associated with a 5-year survival rate of 21-43% (8-10). Likewise, multimodality therapy - radiofrequency ablation (RFA) for CRC liver and pulmonary metastasis combined with resection or chemotherapy - also prolongs survival time (11-13). Newly developed chemotherapeutic agents reduce tumor burden in certain patients to an extent that makes once inoperable tumors resectable with curative intent. Recently introduced targeted molecular agents have also had high response rates.

Such findings suggest that the reduction of tumor volume combined with chemotherapy provides a significant survival benefit in incurable metastatic CRC patients compared with chemotherapy alone. Careful assessment of disease status during chemotherapy combined with an aggressive approach to the treatment of CRC metastases may enable surgical cytoreduction. However, clinical decision-making is complex due to the lack of data on optimal applications of chemotherapy. Thus, the aims of this study are to examine the survival impact of tumor volume reduction using secondary surgery or RFA in patients with metastatic CRC who received chemotherapy, and to discuss the optimal use of chemotherapy in multimodality therapy for advanced CRC.

Patients and methods

This was a retrospective study of all the patients (208 males and females) at our hospital who received chemotherapy for advanced and recurrent CRC between March 2000 and March 2010. The aim was to assess the optimal use of chemotherapy in reducing tumor volume and prolonging survival

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when used in combination with secondary surgery or RFA in patients with metastatic CRC.

Patient selection. Inclusion criteria included histologically proven adenocarcinoma of the colon and rectum. We enrolled patients with unresectable primary, synchronous and metachronous metastatic (recurrent) CRC. We excluded those whose initial treatment consisted of simultaneous primary tumor resection and metastasectomy for synchronous metastasis (e.g., lung and liver). In line with hospital policy for the treatment of CRC metastasis with an unresectable primary tumor, we administered 4-5 months of initial chemotherapy. All patients were informed about multimodality therapy using RFA and/or secondary surgery prior to initial chemotherapy. Multimodality therapy was determined by tumor responses to chemotherapy. The institutional ethics committee approved the study, and written informed consent was obtained from all patients.

Rationale for cytoreduction. Cytoreduction is typically defined as a reduction of tumor volume by therapeutic intervention. There are a number of interventions that reduce tumor volume, e.g., surgical resection, chemotherapy, RFA and radiotherapy. Among these, reductive surgery and RFA may shrink tumor volume 'physically' or 'macroscopically' (at the tissue level) with certainty. In the present study, we defined cytoreduction as a procedure that reduces tumor volume physically using secondary surgery and/or RFA.

Classification of cytoreduction. Cytoreduction is classified according to curability (residual tumor status) and treatment intent. Complete cytoreduction indicates no residual tumor macroscopically or microscopically, with the possibility of a cure. The definition of complete cytoreduction varies by treatment technique. For resection, complete cytoreduction is histopathologically negative resection margins. For RFA, complete cytoreduction is no isotope uptake on PET-CT imaging compared with pre-RFA imaging.

Cytoreduction with maximal debulking intent indicates an attempt to reduce tumor volume as much as possible (incomplete). When maximal debulking cytoreduction leaves a macroscopic or gross residual tumor, effective combination chemotherapy should be performed to attempt complete cytoreduction. For a microscopic residual tumor following maximal debulking cytoreduction, subsequent chemotherapy is expected to completely eradicate it. Repeated cytoreduction is also a feasible option for cure during the course of chemotherapy.

Indications for cytoreduction. Radiological tumor response was measured with MRI and CT scans. Tumor response was evaluated in accordance with the RECIST guidelines (14); a partial response (PR) or stable disease (SD) obtained by systemic chemotherapy indicated consideration of additional surgery and/or RFA for cytoreduction. Multidisciplinary team discussion during chemotherapy determined secondary cytoreductive approaches and timing for each patient. The goal was to achieve potential cure or maximal debulking cytoreduction with minimal treatment stress. The best achieved response rate was reported as patients were scheduled to undergo secondary cytoreduction following assessment scans. A radiologist performed RFA with CT fluoroscopic guidance (X-vigor; Toshiba, Tokyo, Japan) and a RF generator (Cool-tip Radiofrequency Ablation System; Radionics, Burlington, MA, USA) using a single electrode with an internally cooled tip. The details of the RFA approach have been previously described (13).

Chemotherapy. Over a 10-year period, 208 consecutive patients with CRC received 5-FU-, oxaliplatin- or irinotecan-based triple-drug chemotherapy (FOLFOX or FOLFIRI), with or without bevacizumab or cetuximab. Between 2000 and 2005, Japanese national insurance did not allow for the use of oxaliplatin in the treatment of CRC. Thus, the first-line chemotherapy for advanced CRC was 5-FU-based, with or without irinotecan. For patients with no extrahepatic metastasis but with unresectable liver metastases, we used hepatic arterial infusion chemotherapy with 5-FU to achieve conversion chemotherapy, followed by secondary surgery (15).

Drug approval in Japan occurs much more slowly than in the Western world. Since 2005, our first-line chemotherapy has been FOLFOX or FOLFIRI for advanced or recurrent CRC. Molecular targeted agents (including bevacizumab, cetuximab and panitumumab) were approved for use in 2007, 2008 and 2010, respectively. We have been using first-line bevacizumab with FOLFOX or FOLFIRI, our first-line chemotherapy for advanced or recurrent CRC, since 2007. We have also been using second- or third-line cetuximab with or without irinotecan-based chemotherapy since 2008. To improve the resectability of locally inoperable rectal cancer, we used radiotherapy with concurrent 5-FU-based chemotherapy. Following recovery from complete secondary cytoreduction, patients received 5-FU-based adjuvant chemotherapy. Depending on the performance status (PS) of the patient, we reintroduced those with incomplete cytoreduction to chemotherapy.

Statistical analyses. We used JMP version 5 (SAS Institute Inc. Cary, NC, USA) to perform statistical analyses. Contingency tables were analyzed using Fisher's exact test or the χ^2 test with Yates' correction. Associations between continuous variables (interval of cytoreduction, intervening period) and categorical variables (choice of chemotherapy, cytoreductive approach) were evaluated with the Mann-Whitney U Test. Survival curves were constructed according to the Kaplan-Meier method, and differences were analyzed with the log-rank test. $P<0.005$ was considered to be statistically significant. Variables found to be significant at this level were considered to be eligible for logistic regression.

Results

We performed a retrospective review of 208 patients with unresectable primary, synchronous metastatic and metachronous metastatic (recurrent) CRC treated in our department from March 2000 to March 2010. There were 125 males (60%) and 83 females (40%). The mean age was 64 years (range, 13-85 years). A total of 158 patients (76%) had a PS of <2. All patients received chemotherapy initially; 71 of 208 (34%) also had chemotherapy following cytoreduction.

Table I. Outcomes of secondary cytoreduction.

Site of disease	% Cytoreduction rate	% Complete cytoreduction rate	Cytoreductive approach
Unresectable primary tumor	50 (9/18)	44 (4/9)	Resection, 9
Liver metastasis	32 (18/56)	78 (14/18)	Resection. 10/RFA, 15
Lung metastasis	44 (15/34)	67 (10/15)	Resection, 4/RFA, 13
Liver and lung metastases	13 (2/16)	0 (0/2)	RFA, 2
Peritoneal metastasis	28 (14/50)	0 (0/14)	Resection, 14
Local recurrence	55 (12/22)	58 (7/12)	Resection, 9/RFA, 3
Others	8 (1/12)	100 (1/1)	Resection, 1
Total	34 (71/208)	51 (36/71)	Resection, 47/RFA, 33

RFA, radiofrequency ablation.

Table II. Patient characteristics according to cytoreduction.

	Cytoreduction (+) n=71	Cytoreduction (-) n=137	P-value
Age (average)	64	65	ns
Gender (M/F)	46/25	79/58	ns
PS (0:1:2:3:4)	33:28:9:1:0	39:58:23:14:3	0.0305
CEA (<12ng/ml or ≥12 ng/ml)	43/28	59/78	0.0167
Response to treatment (measurable) (CR:PR:SD:PD)	1:41:21:3	5:28:76:26	< 0.0001
Main regimen intended to cause cytoreduction			
5-FU-based	8 (11.3%)	25 (18.2%)	
Hepatic arterial infusion	1 (1.4%)	2 (1.5%)	
CPT-11-based	37 (52.1%)	56 (40.9%)	
Oxaliplatin-based	19 (26.8%)	41 (29.9%)	ns
Molecular targeted agents			
Bevacizumab	8 (11.3%)	11 (8.0%)	
Bevacizumab and/or cetuximab	12 (16.9%)	14 (10.2%)	
Radiation therapy	25/71 (35.2%)	16/137 (11.7%)	<0.0001

ns, not specified; CEA, carcinoembryonic antigen; PS, performance status; CR, complete response; PR, partial response; SD, stable disease, PD, partial disease; 5-FU, 5-fluorouracil.

Table I shows the outcomes of secondary cytoreduction. We used resection and RFA for 47 and 33 lesions, respectively. Of 71 patients, 36 (51%) underwent complete cytoreduction and the remaining 35 (49%) underwent cytoreduction with maximal debulking. Disease sites for cytoreduction were unresectable liver, lung, bladder and peritoneal metastasis. Table II shows baseline patient characteristics with or without cytoreduction.

Patient PS and chemotherapy response were significantly improved in the cytoreduction group compared with the non-cytoreduction group (P<0.0024 and P<0.0001, respectively). The cytoreduction group also had lower serum carcinoembryonic antigen (CEA) levels compared with the non-cytoreduction group (P=0.0164). We observed no significant differences between the groups on the main regimen for cytoreduction, although radiotherapy was frequently administered in the cytoreduction group (P<0.0001).

Median follow-up was 23.1 months. MST of all patients was 26.0 months [95% confidence interval (CI) 23.0 to 29.8 months]. The cytoreduction group had significantly improved survival compared with the non-cytoreduction (chemotherapy alone) group (P<0.0001) (Fig. 1). Cytoreduction resulted in longer overall survival (OS) with a median of 46.0 months (95% CI 38.7 to 91.5 months) versus 20.2 months (95% CI 16.0 to 23.0 months) for chemotherapy alone. Even the incomplete cytoreduction group (n=35) had longer OS than the non-cytoreduction group [MST 38.7 months (95% CI 29.0 to 46.0 months) vs. 20.2 months (95% CI 16.0 to 23.0 months), P<0.0001]. These outcomes indicate that secondary cytoreduction following chemotherapy provides a significant survival advantage for unresectable primary, metastatic or recurrent CRC patients. Table III shows a multivariate analysis of the factors influencing cytoreduction.

Table III. Multivariate analysis of factors influencing cytoreduction.

Variable	OR	95% CI	P-value
CEA (<12 ng/ml or ≥12 ng/ml)	0.600	0.315-1.144	0.1207
Performance status (0/1/2 or 3/4)	6.806	0.849-54.540	0.0709
Response rate (CR/PR or SD/PD)	4.025	2.102-7.707	<0.0001
Radiotherapy (negative/positive)	3.629	1.654-7.962	0.0013

CEA, carcinoembryonic antigen; CR, complete response; PR, partial response; SD, stable disease, PD, partial disease.

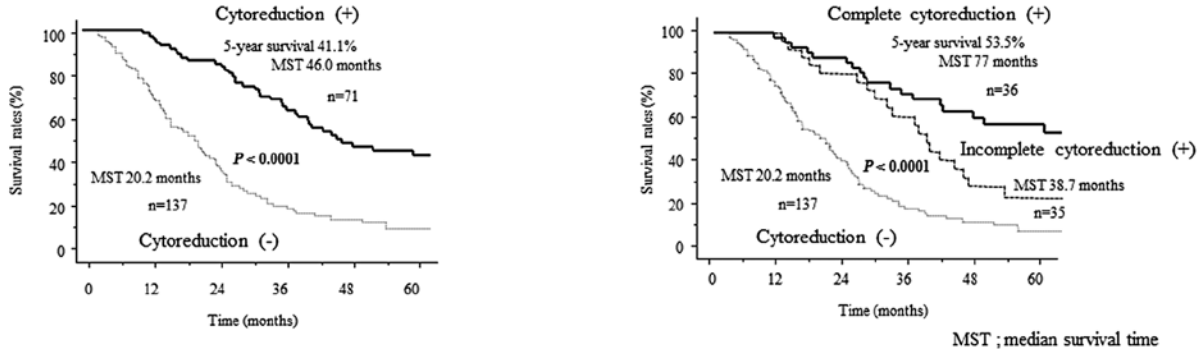

Figure 1. (A) The cytoreduction group had significantly improved survival compared with the non-cytoreduction group (P<0.0001). (B) Overall survival was significantly longer even in the patients in the non-curative cytoreduction group than in those who only received chemotherapy.

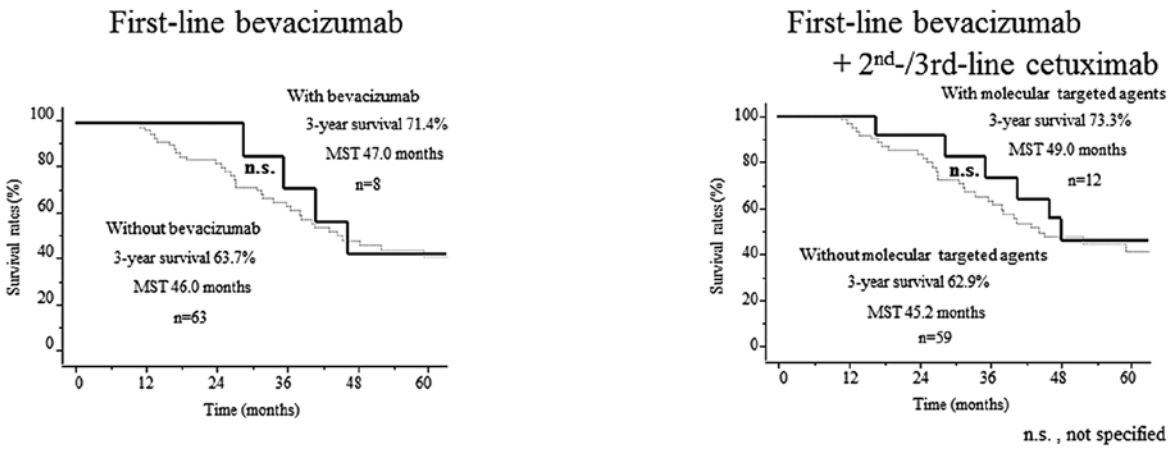

Figure 2. Molecular targeted agents led to a minor but not significant increase in survival in patients who underwent cytoreduction. (A) First-line bevacizumab; (B) first-line bevacizumab with or without second- or third-line cetuximab.

The response rate of chemotherapy was significantly and independently associated with the introduction of cytoreduction. Fig. 2 shows the correlation between molecular targeted therapy and survival in patients who underwent cytoreduction. Molecular targeted agents led to a minor but not significant increase in OS in patients who underwent cytoreduction. The median time between the introduction of initial chemotherapy and cytoreduction was 10 months. First-line bevacizumab enabled the cytoreduction to be introduced earlier than conventional chemotherapy [5.0 months (95% CI 3.3 to 6.4 months) vs. 10.4 months (95% CI 9.4 to 11.9 months), P=0.0028] (Fig. 3), although there were no significant differences in OS between short- (<10 months) and long-interval (≥10 months) cytoreduction (Fig. 4).

In the cytoreduction group, 21 of 71 patients (29.6%) had repeated cytoreductions during treatment. The use of bevacizumab and/or cetuximab correlated with the introduction of re-cytoreduction (P = 0.0167) (Table IV). Fig. 5 shows that the 5-year survival of patients in the re-cytoreduction group was 66.0% (95%CI 58.4 to 73.6%) compared with 32.1% (95% CI 27.1 to 37.1%) in the single cytoreduction group (P=0.0317).

Table IV. Use of molecular targeted agents and re-cytoreduction.

	Molecular targeted therapy n=12 (%)	No molecular targeted therapy n=59 (%)	All patients n=71(%)
Re-cytoreduction (+)	7 (58.3)	14 (23.7)	21 (29.6)
Re-cytoreduction (-)	5 (41.7)	45 (76.3)	50 (70.4)

P=0.0167.

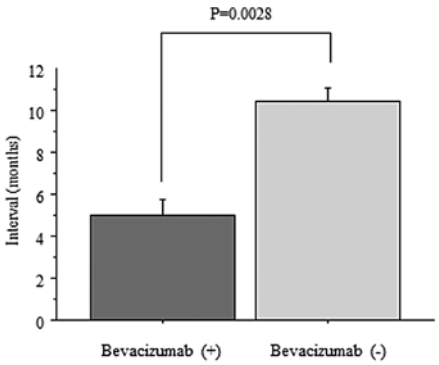

Figure 3. First-line bevacizumab enabled earlier introduction of cytoreduction than conventional chemotherapy (5.0 vs. 10.4 months, P=0.0028).

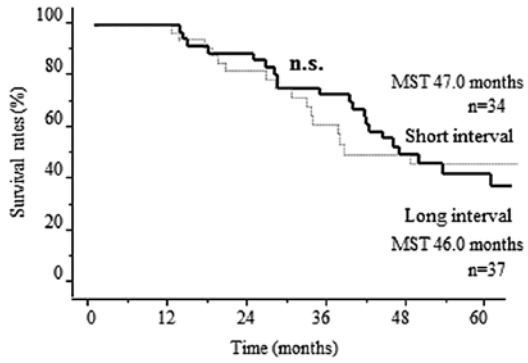

Figure 4. There were no differences in the overall survival of patients with short and long intervals of cytoreduction.

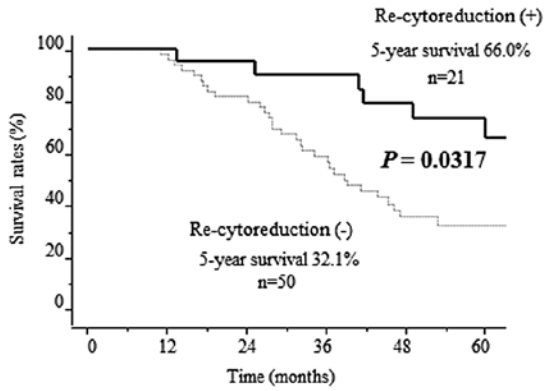

Figure 5. Five-year survival of patients in the re-cytoreduction group was 66.0% compared with 32.1% in patients in the single cytoreduction group (P=0.0317).

Discussion

Treatment of advanced CRC increasingly requires a multimodality approach and multiple treatment options, which add to the complexity of clinical decision-making. Chemotherapy for metastatic CRC may improve survival, lessen symptoms, improve quality of life and shrink liver or lung metastases in patients with potentially resectable disease. Although exposure to all active drugs, including 5-FU/LV, irinotecan and oxaliplatin, during treatment pathways appears to be crucial for increments in survival (16), the optimal use of current chemotherapy in multimodality therapy for advanced CRC remains unknown.

To reduce complexity, we have already proposed the clinical importance of 'de-escalation chemotherapy' concepts for curative intent in the choice of chemotherapy for CRC. 'Escalation chemotherapy' or 'stop and go chemotherapy' are used for palliative purposes (17). De-escalation concepts used to shrink tumor volume and reduce metastases and enable curative surgery for initially inoperable disease should be followed by adjuvant chemotherapy. This is the key to prolonging survival, even after a number of attractive agents, including molecular targeted ones, have been used to treat CRC.

This retrospective study found that CRC patients who had secondary cytoreduction for metastases with surgery and/or RFA following chemotherapy had improved survival compared with patients who had chemotherapy alone. The survival benefit was also observed in patients with incomplete cytoreduction, where the cancer progression was controlled by systemic chemotherapy. The minimally invasive cytoreductive approach with RFA revealed a median intervening period of 1.2 months versus 2.0 months for surgical cytoreduction (P=0.0006). Cytoreduction using RFA enabled us to resume early chemotherapy for patients, which may have helped prolong survival in those with incomplete cytoreduction.

In the present study, the response rate to chemotherapy was the most significant independent factor associated with the introduction of cytoreduction. This finding is consistent with the study by Folprecht *et al* regarding unresectable liver metastases (18). High response rates in our study population may be due to the overall good PS of the group. Furthermore, the results showed the usefulness of cytoreduction during chemotherapy in not only liver metastases but also other tumor sites, such as lung, peritoneal and local recurrences.

Recent molecular targeted therapies demonstrate a high response rate and appear very attractive for cytoreduction. Thus, we used the delayed approval of anticancer drugs in

Japan to evaluate the significance of additional molecular targeted agents on 'de-escalation chemotherapy' concepts for CRC. In multimodality therapy, first-line bevacizumab enabled cytoreduction to be introduced earlier than conventional chemotherapy (5.0 vs. 10.4 months). The median time to cytoreduction was equivalent to that of the CELIM trial, which examined the effectiveness of cetuximab and FOLFOX6 or FOLFIRI in the neoadjuvant treatment of unresectable colorectal liver metastases. R0 or R1 resection and/or RFA was performed in 46% of all patients, and the median time to cytoreduction was 5.1 months (19).

In the present study, there were no differences in the OS of those with short- (<10 months) and long-interval (≥10 months) cytoreduction. However, the first-line use of bevacizumab and/or second- or third-line use of cetuximab correlated with the introduction of re-cytoreduction. Patients who received re-cytoreductive surgery had significantly improved survival compared with those in the single cytoreduction group. This suggests that first-line bevacizumab and/or second- or third-line cetuximab may contribute, at least in part, to the prolonged time to progression from early initial and repeated cytoreductions.

Our protocol may limit the generalizability of our findings, yet they clearly show that patients who received chemotherapy alone had a far shorter MST time than those who had cytoreduction following chemotherapy. It could be that the longer survival of those in the cytoreduction group came from additional cytoreduction based on chemotherapy. The results show that cytoreduction is necessary as one of the multimodality treatments, and may provide the only chance of cure for patients with unresectable metastatic CRC.

In conclusion, with a number of lines of treatment now available, initial aggressive chemotherapy leading to cytoreduction may be a feasible treatment option. Our data show that cytoreduction following chemotherapy is associated with further prolongation of survival in patients with multimodality therapy for advanced CRC.

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