

# Synchronous liver metastases in patients with rectal cancer: can we establish which treatment first?

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## Introduction

Colorectal cancer (CRC) affects nearly 1.4 million new patients each year worldwide.<sup>1</sup> The treatment algorithm for local or locally advanced colon and rectal cancer (RC), and also for patients with never-resectable metastases, is well established.<sup>2–4</sup> However, the optimal strategy in patients with synchronous metastasis is more controversial and, especially in patients with RC, several modalities must be combined to achieve the most favorable outcome. Before the introduction of total mesorectal excision (TME) a local recurrence was frequently seen in 30–40% of patients with locally advanced RC.<sup>5</sup> Neoadjuvant long-course chemo-radiation (LC-CRT) or short-course radiotherapy (SC-RT) followed by appropriate TME has reduced local recurrence (LR) rates to 5% or even less as shown not only in randomized trial with selected patients but also in population cohorts.<sup>6,7</sup> However, the role and timing of neoadjuvant radiation is less well defined in patients presenting with synchronous metastasis. Randomized studies have focused on one treatment modality (e.g. preoperative LC-CRT or SC-RT in patients with resectable RC or chemotherapy in the setting of widespread nonresectable metastatic disease) but the sequence of different modalities (surgery, chemotherapy, and radiation) has not been studied in a randomized strategy trial. Based on lack of consensus regarding the optimal sequence of surgery, systemic therapy and radiotherapy for patients with stage 4 RC treated with curative intent, a ‘multidisciplinary session: synchronous liver metastases in RC: which treatment first?’ was organized by the

European Society for Medical Oncology (ESMO) and presented during the ESMO 2017 conference in Madrid, Spain. Three distinct lectures focused on the radiation therapy perspective, the surgical oncology perspective, and the medical oncology perspective. The present paper is a summary of those three lectures with focus on a multidisciplinary approach and with an update on recent literature.

## All patients must be evaluated by a multidisciplinary team

Many strategies are possible in patients with RC with synchronous metastases. There are numerous overviews but no randomized trial to guide us on the optimal strategy. A network meta-analysis (no phase III study) including 3605 patients with synchronous colorectal liver metastases (CRLM) demonstrated no clear statistical surgical outcome or survival advantage toward any particular strategy.<sup>8</sup> Therefore, selecting the optimal treatment strategy in patients with synchronous metastatic RC is a difficult task due to lack of good evidence. There are trials evaluating systemic therapy in patients with metastatic CRC (mCRC) and there are trials with radiotherapy for patients with localized RC but there are no trials for patients with both manifestations. In particular, there are no randomized trials to evaluate the best sequence of therapy and no widely accepted standard of treatments. Thus treatment is not evidence based but mainly rests upon expert opinion and short-term oncological goals.

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There are at least four scenarios for the management of patients with synchronous metastatic RC. In patients with resectable CRLM, the primary could be asymptomatic or symptomatic. Similarly, in patients with nonresectable CRLM the primary could also be asymptomatic or symptomatic. The decision for timing of the resection of either the primary or the CRLM should be individualized for each patient, considering technical, oncological and patient factors. An alternative approach in addition to 'liver first' or 'rectal first' is 'the interval strategy' that involves the administration of LC-CRT followed by the resection of the CRLM in the interval between RT and rectal surgery.<sup>9,10</sup> For these reasons, all patients must be evaluated by a specialist multidisciplinary team (MDT).

At the MDT, the following questions must be asked: what is the burden of metastatic disease? Are there other sites of metastases, and if so, are these extrahepatic metastases potential curable (e.g. a small resectable lung metastases)? There should be a detailed magnetic resonance imaging (MRI) assessment of the primary, and the performance status and the patient's comorbidity must be well known. There is a need for randomized controlled trials to further investigate the optimal treatment strategy in patients with synchronous metastatic RC (mRC).

Analysis of the Surveillance, Epidemiology and End Results database including more than 60,000 patients from 1988 to 2010 showed that the majority of patients with mCRC had undergone primary tumor resection but beginning in 2001, there was a trend toward fewer resections.<sup>11</sup> Despite a declining resection rate, an increased overall survival (OS) was found. A recent individual patient data analysis of trials in mCRC showed an improved survival in synchronous mCRC patients if the primary was resected.<sup>12</sup> Such analyses are open to bias because the reasons that resection is not performed are not available. Hence, presently, it's not known whether the primary should be resected or not. Several randomized studies like CAIRO4 are evaluating this problem in patients receiving palliative therapy but if the overall aim is cure then the primary must of course be resected.

In patients with easy resectable primary and CRLM, perioperative FOLFOX before and after liver resection is the recommended treatment strategy, and in selected cases, the primary may be

resected concurrently.<sup>3</sup> Recommendations are to administer chemotherapy for a total of at least 6 months.

In patients with nonresectable liver-limited CRLM, patients should start with best systemic therapy and patients should be restaged and evaluated by the MDT every 2 months.

The classical way of treating patients with RC and metastases was to start with LC-CRT and then resect the primary. The major problem with this strategy is that administration of effective systemic treatment is postponed for months and during this period, there is a risk of further progression of metastatic disease which may convert potential curable disease to never-resectable disease. At the ESMO consensus meeting, all participants agreed on upfront chemotherapy in case of metastatic disease and asymptomatic primary.<sup>2</sup>

### Magnitude of the problem

How many patients with RC are diagnosed with synchronous metastasis? In a nationwide study covering 98% of Swedish RC cases from 2007 to 2011 (total 9158 patients), it was found that 20% of patients had mRC at the time of diagnosis, 75% of mRC patient had synchronous liver metastases and one half had liver-limited disease (LLD). Resection rate was 23% in RC patients with LLD, however, with huge variation from 8.5% to 32.1% between regions.<sup>13</sup> Preoperative chemotherapy was administered to 33% of patients who had resection.

### Efficacy of systemic therapy on colorectal liver metastases

According to the current ESMO consensus guidelines,<sup>3</sup> a preoperative strategy with FOLFOX may be used in patients with good prognosis and easily resectable metastasis but if a conversion or down-sizing strategy is recommended by the MDT then the best systemic therapy must be initiated. It is well known that a higher overall response rate (ORR) increases the chance for resection of CRLM<sup>14,15</sup> and therefore a combination that produces the highest ORR is recommended in fit patients. In general, double regimens (e.g. FOLFOX, FOLFIRI, CapOx) compared with monotherapy, and triplet regimens (e.g. FOLFOXIRI) compared with double regimens produce higher ORRs.<sup>3</sup>

**Table 1.** Doublet chemotherapy with or without anti-EGFR in patients with RAS wild-type metastatic colorectal cancer.<sup>[16-19]</sup>

Authors (trial name)	Regimen	N	RR (%)	Δ % RR	PFS (mo)	Δ PFS (mo)	OS (mo)	Δ OS (mo)
Van Cutsem, (CRYSTAL) JCO 2015	FOLFIRI	189 <sup>§</sup>	39	+28	8.4	+3.0	20.2	+8.2
	FOLFIRI + Cet	178 <sup>§</sup>	66*		11.4*		28.4*	
Bokemeyer, (OPUS) EJC 2015	FOLFOX	49 <sup>§</sup>	29	+28	5.8	+6.2	17.8	+2.0
	FOLFOX + Cet	38 <sup>§</sup>	56*		12.0*		19.8	
Douillard, (PRIME) NEJM 2013	FOLFOX	253 <sup>§</sup>	48	+9	7.9	+2.2	20.2	+5.6
	FOLFOX + Pan	259 <sup>§</sup>	57*		10.1*		25.8*	
Qin, (TAILOR) ESMO 2016	FOLFOX	200 <sup>‡</sup>	40	+21	7.4	+1.9	17.8	+2.9
	FOLFOX + Cet	193 <sup>‡</sup>	61*		9.2*		20.7*	

\*Significant difference.

§Retrospective evaluation of RAS status.

‡All patients were RAS wildtype at inclusion.

RR, response rate; PFS, progression-free survival; OS, overall survival; Cet, cetuximab; Pan, panitumumab.

When epidermal growth factor receptor (EGFR) inhibitors (cetuximab or panitumumab) are added to combination regimens like FOLFIRI or FOLFOX, all efficacy parameters are improved (Table 1); ORRs are increased and progression-free survival (PFS) and OS are prolonged but this benefit is restricted to patients who are RAS wildtype and BRAF wildtype.<sup>16-19</sup> A similar consistency has not been observed when bevacizumab was added to modern regimens<sup>3</sup> and in the largest randomized study, bevacizumab did not improve ORR.<sup>20</sup> Nevertheless, the optimal combination of chemotherapy and targeted therapy has been discussed for many years. Three studies have directly compared efficacy of EGFR inhibitors and bevacizumab in mCRC patients (Table 2A). In the randomized phase III FIRE-3,<sup>21,22</sup> the primary endpoint, ORR, was not achieved but the secondary endpoint, OS, was significantly longer, particularly in the subgroup with RAS and BRAF wildtype tumors. In the randomized phase II PEAK study,<sup>23</sup> there was a significantly longer PFS and numerically longer OS, but no difference in ORR. In CALGB 80405, double chemotherapy with cetuximab resulted in higher ORR but with no significant difference in PFS or OS.<sup>24,25</sup> Several studies have shown that left-sided CRC are more dependent on EGFR-related pathways and therefore it was evident to do subgroup

analysis in patients with left-sided tumors (Table 2B). Within this subgroup analysis, the picture became much more homogenous showing higher ORR and prolonged OS in patients with left-sided primary (including rectal) treated with EGFR inhibitors compared with bevacizumab.<sup>26,27</sup> In the two reviews, it was concluded that the preferred treatment option in patients with left-sided RAS and BRAF wildtype tumor is doublet chemotherapy with EGFR inhibitors.

A number of randomized studies have evaluated triplet chemotherapy in patients with mCRC, often unselected by stage and tumor biology but elected by younger age and excellent performance status (Table 3A). Two Italian phase III trials<sup>28,29</sup> showed that triplet chemotherapy, with or without bevacizumab, increased ORR and prolonged PFS and OS. Other studies have shown comparable and promising results. Bevacizumab was added to all combinations and we can therefore only conclude that triplet chemotherapy with bevacizumab is tolerable but the additional benefit of bevacizumab cannot be evaluated from these studies. In the OLIVIA trial,<sup>30</sup> in which mCRC patients with LLD were included, triplet chemotherapy with bevacizumab produced an impressive ORR of 81% (Table 3A). Consistently, all studies evaluating triplet chemotherapy with bevacizumab produced a high ORR of at least 60%.

A number of phase II studies have combined triplet chemotherapy with EGFR inhibitors, mainly including mCRC KRAS wildtype (Table 3B). All studies showed a very high ORR of more than 70%, but the additional benefit of EGFR inhibitors cannot be evaluated. The first study to evaluate triplet chemotherapy with or without targeted therapy was presented at ESMO 2017. In a randomized phase II trial, patients with RAS wildtype mCRC patients were randomized to modified FOLFOXIRI ± panitumumab.<sup>40</sup> The authors found that triplet + panitumumab produced a significant higher ORR (86% versus 61%), not only in left-sided tumors but also with right-sided location. Unpredictably they also found a high ORR (71%) in patients with BRAF-mutated tumors.

### Efficacy of systemic therapy on the primary cancer

ORR in patients with metastatic disease is close to 50%<sup>3</sup> but what is the response rate in the primary to systemic therapy? It is difficult to measure tumor shrinkage in the primary according to RECIST 1.1, since it arises in a hollow distensible organ and the longest diameter can hardly be defined on axial images, but regression in the primary is comparable with that seen in metastatic sites. However, perhaps pathological complete response (pCR) is a more relevant measure, since it is reproducible and there is an excellent correlation with OS.<sup>41</sup> After RT and delayed surgery, a pCR of around 10% can be expected, but this increases to around 15% if chemotherapy, mainly

**Table 2A.** Bevacizumab or anti-EGFR in patients with RAS wild-type/BRAF wild-type metastatic colorectal cancer.<sup>[22-24]</sup>

Authors (trial name)	Regimen	N	RR (%)	Δ % RR	PFS (mo)	Δ OS (mo)	OS (mo)	Δ OS (mo)
Stintzing (FIRE-3) Lancet Onc 2016	FOLFIRI + Bev	201	59	+6	10.2	+0.1	25.0	+8.1
	FOLFIRI + Cet	199	65		10.3		33.1*	
Schwartzberg (PEAK) JCO 2014	FOLFOX + Bev	82	61	+3	9.5	+3.5	28.9	+12.4
	FOLFOX + Pan	88	64		13.0*		41.3	
Venook (CALGB 80405) JAMA 2017	Double + Bev	256	54	+15	11.3	+0.1	31.2	+0.8
	Double + Cet	270	69*		11.4		32.0	

\*Significant difference.

Unselected according to primary location. Results are shown as difference in efficacy to substantiate the difference in effect.

Bev, bevacizumab; Cet, cetuximab; OS, overall survival; Pan, panitumumab; PFS, progression-free survival; RR, response rate.

**Table 2B.** Bevacizumab or anti-EGFR in left-sided RAS wild-type/BRAF wild-type metastatic colorectal cancer.<sup>[22,23,25]</sup>

Authors (trial name)	Regimen	N	RR (%)	Δ % RR	PFS (mo)	Δ OS (mo)	OS (mo)	Δ OS (mo)
Stintzing (FIRE-3) Lancet Onc 2016	FOLFIRI + Bev	149	62	+7	10.7	0	28.0	+10.3
	FOLFIRI + Cet	157	69		10.7		38.3*	
Schwartzberg (PEAK) JCO 2014	FOLFOX + Bev	54	57	+7	11.5	+3.1	32.0	+11.4
	FOLFOX + Pan	53	64		14.6		43.4	
Venook (CALGB 80405) ASCO 2016	Double + Bev	152	58	+11	11.2	+1.5	32.6	+6.7
	Double + Cet	173	69*		12.7		39.3*	

\* Significant difference

Bev, bevacizumab; Cet, cetuximab; OS, overall survival; Pan, panitumumab; PFS, progression-free survival; RR, response rate.

**Table 3A.** Randomized trials evaluating triplet chemotherapy with or without bevacizumab in patients with metastatic colorectal cancer unselected for RAS status.<sup>[28-33]</sup>

	Falcone (GONO), JCO 2007		Cremolini (TRIBE), Ann Oncol 2015		Bendell (STEAM), JCO 2016			Schmoll (CHARTA), ASCO 2017		Falcone (MOMA), Ann Oncol 2016		Gruenberger (OLIVIA), Ann Oncol 2014	
	FOLFIRI n = 122	TRIPLE n = 122	FOLFIRI Bev n = 256	TRIPLE Bev n = 252	FOLFOX Bev n = 95	sTRIPLE Bev n = 92	cTRIPLE Bev n = 93	FOLFOX Bev n = 121	TRIPLE Bev n = 121	TRIPLE Bev n = 117	TRIPLE Bev n = 115	FOLFOX Bev n = 39	TRIPLE Bev n = 41
Age (years)	64	62	60	60	58	56	58	62	60	61	62	57	63
PS 0, %	61%	61%	90%	90%	54%	57%	67%	47%	53%	85%	85%	80%	56%
RR (%)	41	66*	53	65*	47	62	60	61	70	68	58	62	81*
PFS (months)	6.9	9.8*	9.7	12.3*	9.5	11.4	11.9	10.3	12.0	9.5	10.6	11.5	18.6
OS (months)	16.7	22.6*	25.8	29.8*	30.7	28.3	34.0	24.0	28.0	-	-	-	-

\* Significant difference

cTRIPLE, continuous TRIPLE; OS, overall survival; PFS, progression-free survival; PS, performance status; sTRIPLE, sequential TRIPLE; TRIPLE, combination of 5-fluorouracil, oxaliplatin, and irinotecan.

**Table 3B.** Triplet chemotherapy with anti-EGFR in metastatic colorectal cancer.<sup>[34-40]</sup>

	Garufi (POCHER), BJC 2010	Assenat (FRENCH), Oncologist 2011	Folprecht (GERMAN), BMC Cancer 2014	Saridaki (GREEK) BJC 2012	Fornaro (TRIP), Ann Oncol 2013	Cremolini (MACBETH), JAMA Oncol 2018		Geissler (VOLFI), Ann Oncol 2017	
	TRIPLE Cet n = 43	TRIPLE Cet n = 42	TRIPLE Cet n = 20	TRIPLE Cet n = 30	TRIPLE Pan n = 37	TRIPLE Cet n = 59	TRIPLE Cet n = 57	TRIPLE n = 33	TRIPLE Pan n = 63
RR (%)	79	81	75	70	89	68	75	61	86*
PFS (months)	14	9.5	16	10.2	11.3	11.2	9.3	10.5	10.8
OS (months)	37	24.7	33	30.3	-	-	-	-	-

\* Significant difference

Cet, cetuximab; OS, overall survival; Pan, panitumumab; PFS, progression-free survival; RR, response rate; TRIPLE, combination of 5-fluorouracil, oxaliplatin, and irinotecan.

5-fluorouracil (5-FU), is used as a radiation sensitizer. If systemic therapy is added after SC-RT or LC-CRT, a pCR of at least 20% can be achieved. Garcia-Aguilar and colleagues conducted four consecutive phase II trials in patients with localized RC, and after LC-CRT, they added sequentially more and more cycles of FOLFOX and found that LC-CRT followed by 3 months of FOLFOX resulted in a pCR of 38%.<sup>42</sup>

The traditional method for treating high-risk primary RC includes the delivery of neoadjuvant LC-CRT followed by TME. However, the use of preoperative chemotherapy as an alternative has increased in popularity and is presently being studied in ongoing trials. Preoperative chemotherapy has the potential to impact on the viability of distant micrometastases early in the evolution of the disease, and could thereby reduce systemic failures, in addition to facilitating local control by surgical resection, avoiding the long-term toxic effects of CRT. A number of small studies have evaluated pCR rate after chemotherapy without RT.<sup>43-48</sup> Response rate is more than 50% in all studies and pCR is around 15% (range from 5% to 25%). Perhaps even more interesting, the risk of PD is 0%, except for one study where one patient developed PD during therapy: thus, the response to preoperative chemotherapy could also select patients for either CRT or upfront surgery, which should result in decreased morbidity for some patients.

These promising data may question the use of RT in patients with metastatic RC but until more solid data are available, we will recommend SC-RT if the strategy is with curative intent. This is supported by data from a Chinese randomized

three-arm phase III including almost 500 patients with locally advanced RC.<sup>49</sup> Patients were essentially randomized to LC-CRT (with 5-FU), LC-CRT (with FOLFOX), or FOLFOX without RT. Preoperative FOLFOX alone resulted in lower pCR rate than LC-CRT (the rate of pCR was 14%, 28%, and 7%, respectively) but there was no difference in R0 resection rate (around 90% in all three arms).

### Efficacy of radiotherapy on the primary cancer

Classically, there are two possible choices for preoperative radiotherapy: SC-RT (25 Gy/5 fractions) or LC-CRT (45–50.4 Gy/25–28 fractions), which are equally effective in resectable cancers.<sup>4,50-51</sup> Preoperative RT induces pCR in around 15% without clear-cut difference in frequency between LC-RT and SC-RT if there is a planned delay of 6–8 weeks before surgery to allow shrinkage of the primary tumor. In the Stockholm III trial, there was no difference in local recurrence rate after SC-RT or LC-RT if surgery was delayed in both situations.<sup>52</sup>

The short overall treatment time (OTT) of SC-RT, usually in 5 consecutive days with immediate surgery, is a highly flexible treatment strategy, which is associated with high compliance and low toxicity, in part reflecting an insufficient interval to express the normal tissue reactions and systemic inflammatory effects from radiation before the rectum is surgically removed.<sup>6,53</sup>

There are at least two questions in RC patients with CRLM. Do patients need radiotherapy at all



and if so, which out of SC-RT or LC-CRT? Findings from a pooled analysis of individual patient data from several institutions<sup>41</sup> showed that patients who obtained a pCR after preoperative LC-CRT had a significantly longer OS than those with residual disease and this may be an argument for recommendation of RT even in patients with synchronous mRC.

### **Is there a role for radiotherapy to the primary tumor in patients with resectable stage IV rectal cancer?**

Patients are unlikely to be cured without surgery and patients are less likely to be cured without chemotherapy. Radiotherapy has only a minor impact on curability, but so far, RT is indicated if the plan is to resect metastases and the primary. Otherwise, RT is only indicated in the case of palliation of symptoms. In a phase II study in patients with near-obstruction lesions, SC-RT and chemotherapy allowed most patients to avoid surgery even those with near-obstruction lesions.<sup>54</sup> In the RAPIDO trial, patients with 'high-risk RC' were randomized to standard LC-CRT or SC-RT followed by 6 cycles of CapOx before TME.<sup>55</sup> Unfortunately, results from the RAPIDO trial will not be available until 2020.

What is the downside of radiotherapy? LC-CRT may delay the application of full doses of chemotherapy or worsen the compliance to systemic doses of chemotherapy. However, SC-RT can be administered between full doses of systemic therapy with no or only minimal delay of administration. SC-RT combined with systemic therapy has primarily been used in Europe but the first US experience with SC-RT as part of the multidisciplinary management of mRC has recently been reported with promising results.<sup>56</sup>

### **Timing of resection of the liver metastasis and the rectal cancer**

If a patient presents either with resectable liver metastasis or is converted to resectable disease after systemic therapy, the timing of liver resection is more crucial than the resection of the primary. We have learned throughout the last 15 years that patients should get their resection of liver metastasis as soon as possible after evaluating the benefit of systemic therapy. Interestingly, the more aggressive/effective the therapy is, the faster a resection can be offered. In the background is the fact that the remaining liver after

resection has to recover and function quickly especially after major hepatectomy. Evaluable literature clearly demonstrates that length of chemotherapy correlates with morbidity and mortality after liver resection.<sup>57</sup> In the only prospective international trial evaluating the systemic therapy potential to convert unresectable LLD into resectable disease, two patients died due to liver failure after receiving more than 6 months of treatment.<sup>30</sup> We therefore advocate repeat MDT discussions every 2 months to identify resectable patients as soon as possible.

Timing of resection of the rectal primary is crucial on two points: first, the best waiting period on maximum local remission after RT or CRT in resectable RC and second, the best downsizing therapy prior to potential curative resection in initially locally advanced noncurable resectable disease.

### **Conclusion**

The optimal sequence and use of the individual modalities remain undefined, but should be employed on an individual basis. Multidisciplinary approach and decision making are essential in patients with RC and synchronous metastases. In the MDT, the treatment aim must be defined upfront and there should be a regular follow up with re-evaluation and rediscussion every 2 months.

Unless the primary and the few liver metastases are 'easily resectable', we recommend beginning with the most effective systemic chemotherapy (often triplet chemotherapy with targeted therapy, depending on RAS status) with re-evaluation at the MDT every 2 months. We also recommend liver surgery first as soon as CRLM becomes resectable and to continue systemic treatment before (and perhaps after) resection of the primary for a total of at least 6 months. SC-RT can be added to systemic chemotherapy at virtually any point with no or minimal delay.

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### **Conflict of interest statement**

The authors declare that there is no conflict of interest.

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