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Potentially resectable metastatic colorectal cancer: An individualized approach to conversion therapy

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Highlights

•Patients with metastatic colorectal cancer may benefit from radical surgery.

•Conversion therapy is essential for the possible shift from unresectable to resectable disease.

•A tailored approach is possible considering patient and disease's factors.

•Patients presenting with colorectal cancer metastases should be evaluated for multimodal management with curative intent.

Abstract

Colorectal cancer is one of the most common cancers worldwide. In recent years, the survival of patients with metastatic disease has improved due to the developments in both medical and surgical care. Patients with technically unresectable metastatic disease could benefit from a multidisciplinary approach for their possible shift toward a technically resectable condition; the choice of the most effective systemic treatment is then crucial to allow conversion to resectability. Systemic conversion therapy may include chemotherapy agents' combinations (fluoropyrimidine, irinotecan and oxaliplatin), with or without targeted agents (cetuximab, panitumumab, bevacizumab). The choice of the best treatment option has to be evaluated by taking into account each patient's baseline characteristics, biological and pathological information and surgical strategy. In particular, the role of some biologic characteristics of the disease, namely the mutational status of EGFR-pathway oncogenes, is emerging as an important predictive factor of response to anti-EGFR targeted agents. Patients presenting with colorectal cancer metastases should be evaluated for multimodal management with curative intent as the appropriate chemotherapy regimen may induce tumor shrinkage, conversion to resectability and improved survival

Background

Colorectal cancer (CRC) is one of the leading causes of death from cancer worldwide [1]. In recent decades, the survival of patients with metastatic CRC (mCRC), has dramatically improved due to the developments in both medical and surgical care [2]. In selected patients, surgery can be included in the treatment plan, as the resection of hepatic metastases improves progression-free survival (PFS) and may offer the chance for cure in approximately 10–25% of patients [[2], [3],[4], [5], [6], [7], [8]].

A thorough evaluation must be carried out to determine the appropriate treatment strategy for every patient diagnosed with mCRC. A first analysis should be made to distinguish between patients with oncologically non-resectable disease (such as those with multiple sites of metastatic disease), who will never be considered for surgery even after responding to medical therapy, from patients with technically unresectable metastases, who are regarded as "temporarily" unresectable, and must be carefully evaluated in the course of primary systemic treatment for their possible shift (conversion) toward a technically resectable condition. Indeed, at present the definition of resectability is solely technical and based on the possibility to completely resect all visible metastases leaving an adequately functioning parenchyma [9]. This definition of resectability, by excluding all tumor features, implies that each patient must have its disease managed by a multidisciplinary team, including medical oncologist, radiologist, interventional radiologist, and radiation therapist, where all the specialists involved can correctly define the resectability status [10] and reassess the surgical option in case of tumor response.

Regarding systemic therapy, medical treatment, administered in the case of primarily unresectable disease, which is capable of converting the disease to a resectable status, is generally referred to as "conversion therapy".

In this review we overview the possible therapeutic options for patients with initially unresectable mCRC, focusing on individualized approaches to conversion therapy in a multidisciplinary strategy.

Conversion therapy

Since the 1980s, chemotherapy for CRC has been based on fluoropyrimidine-5-fluorouracil (5-FU), alone or in combination with leucovorin (LV). Advances in clinical research have progressively led to the use of newer agents, namely irinotecan and oxaliplatin as chemotherapy drugs, and cetuximab, panitumumab, bevacizumab, aflibercept and regorafenib as targeted agents [[11], [12], [13], [14]].

Most of the results in terms of efficacy and tumor shrinkage can be extrapolated from studies that used different chemotherapy regimens in the palliative setting. The majority of patients enrolled had an "oncologically unresectable" disease, being PFS or overall survival (OS) the primary endpoint. The metastasis resection and conversion rates were then evaluated retrospectively and no clear definition of resectability was provided. The efficacy of chemotherapeutic associations in doublets or triplets has been established [[15], [16], [17], [18], [19], [20], [21]] and afterwards, also the association between chemotherapy and monoclonal antibodies has proven to be effective [[13], [22], [23], [24], [25], [26],[27], [28], [29], [30], [31], [32], [33], [34], [35], [36]]. The results in terms of OS and overall response rate (ORR) of the main phase II and III studies are summarized in Table 1.

Author	Phase	N of patients	Regimen	ORR (%)	OS (months)
Table 1 Results in terms of overall survival and overall response rate of main phase II and III studies.					
De Gramont 2000	III	420	5-FU + leucovorin	21.9	16.2
			5-FU + leucovorin + oxaliplatin	50	14.7
Giacchetti 2000	III	200	chrono5-FU + leucovorin	16	19.9
			chrono5-FU + leucovorin + oxaliplatin	53	19.4
Douillard 2000	III	387	5-FU + leucovorin	22	14.1
			5-FU + leucovorin + irinotecan	35	17.4
Saltz 2000	III	683	5-FU + leucovorin+ irinotecan	50	14.8
			5-FU + leucovorin	28	12.6
			irinotecan	29	12
Goldberg 2004	III	795	IFL	31	15
			IROX	35	17.4
			FOLFOX	45	19.5
Colucci 2005	III	360	FOLFIRI	31	15
			FOLFOX4	34	14
Van Cutsem 2009	III	1198	FOLFIRI + cetuximab	46.9 (59.3)[a]	19.9 (24.9)[a]
			FOLFIRI	38.7 (43.2)[a]	18.6 (21)[a]
Bokemeyer 2009	III	337	FOLFOX4 + cetuximab	46 (61)[a]	NA
			FOLFOX4	36 (37)[a]	NA
Folprecht 2010	III	111	FOLFOX6 + cetuximab	68	=
			FOLFIRI + cetuximab	57	=
Maughan 2011	III	1630[a]	FOLFOX/XELOX	57	17.9
			FOLFOX/XELOX + cetuximab	64	17
Ye 2013	III	138[a]	FOLFIRI/FOLFOX + cetuximab	57.1	30.9
			FOLFIRI/FOLFOX	29.4	21

Douillard 2010	III	1183	FOLFOX4 + panitumumab	55[a]	23.9[a]
			FOLFOX4	48[a]	19.7[a]
Leone 2013	III	49 (35)[a]	XELOX + panitumumab	54 (87,5 DCR[a])	21.9
Schwartzberg 2012	II	245[a]	FOLFOX6 + panitumumab	58	NR
			FOLFOX6 + bevacizumab	54	25.4
Hurwitz 2004	III	813	IFL + bevacizumab	44.8	20.3
			IFL	34.8	15.6
Saltz 2008	III	1401	FOLFOX/XELOX + bevacizumab	38	21.3
			FOLFOX/XELOX + placebo	38	19.9
Van Cutsem 2009	EA	1914	FOLFOX/XELOX/XELIRI/5-FU + bevacizumab	NA	22.7
Wong 2011	II	46	CAPOX + bevacizumab	78	NA
Souglakos 2002	II	31	Irinotecan + oxaliplatin + 5-FU/LV	58.1	NR
Falcone 2002	II	42	Irinotecan + oxaliplatin + 5-FU/LV	69	26.5
Masi 2004	II	32	FOLFOXIRI	72	28.4
Souglakos 2006	III	285	FOLFIRI	33.6	19.5
			FOLFOXIRI	43	21.5
Falcone 2007	III	244	FOLFIRI	34	16.7
			FOLFOXIRI	60	22.6
Garufi 2010	II	43	chronoIFLO + cetuximab	79.1	37 (stim)
Assennat 2011	II	42	FOLFIRINOX + cetuximab	80.9 (83.3)[a]	24.7 (NR)[a]
Saridaki 2012	II	30[a]	FOLFOXIRI + cetuximab	70	30.3
Fornaro 2013	II	37[a]	FOLFOXIRI + panitumumab	89	NR
Loupakis 2013	III	508	FOLFIRI + bevacizumab	53	NA
			FOLFOXIRI + bevacizumab	64	NA
Gruenberger 2013	III	80	mFOLFOX6 + bevacizumab	61.5	NA
			FOLFOXIRI + bevacizumab	80.5	NA

Heinemann 2013	III	592[a]	FOLFIRI + cetuximab	62	28.5
			FOLFIRI + bevacizumab	57	25
Bruera 2012	II	50[a]	FirBFox	84	23

ORR, overall response rate; OS, overall survival; 5-FU, 5-fluorouracil; EA, expanded access; NA, not assessed; NR, not reached.

a KRAS wt population.

Several studies have investigated the use of different schemes in the specific setting of conversion therapy; all these trials have explored the association of chemotherapy with monoclonal antibodies (MoAbs).

The phase II BOXER trial evaluated bevacizumab, a MoAb against VEGF, in association with a capecitabine and oxaliplatin (CAPOX) chemotherapy regimen in patients ineligible for upfront surgery, which resulted in an ORR of 78%. The conversion rate in this trial reached 40%, with 12 out of 30 patients judged to be resectable after treatment [35].

In the randomized phase II trial OLIVIA, bevacizumab was evaluated in association with mFOLFOX6 or FOLFOXIRI. The response rate (RR) was higher in the FOLFOXIRI-bevacizumab arm (80.5% vs. 61.5% in the FOLFOX arm; p = 0.061). Although this value did not reach statistical significance, radical (R0) resection rate was significantly higher in the FOLFOXIRI-bevacizumab arm (48.8% vs. 23.1%; p = 0.017) [27].

Other studies evaluated the use of anti-EGFR monoclonal antibodies in the conversion setting. As will be further discussed below, during the clinical development of these drugs (cetuximab particularly) the mutational status of KRAS was recognized as a predictive marker of response to therapy. As a result, in older studies, patients were unselected and the evaluation in the KRAS wild type (KRASwt) population was performed retrospectively.

The CELIM phase II randomized trial compared the association of cetuximab with FOLFIRI and FOLFOX6 in patients with non-resectable liver metastases. The difference between the two groups, in terms of RR, was not significant. Tumor response, evaluated in a retrospective analysis, was significantly higher in patients with KRASwt tumors (70% vs. 41%, p = 0.008). R0 resection was possible in 38% of patients in FOLFOX6-cetuximab arm and 30% of patients in FOLFIRI-cetuximab arm. According to the retrospective review, resectability rates increased from 32% at baseline to 60% after chemotherapy (p < 0.0001), regardless of the regimen used [37].

In a recent phase II randomized trial, patients with KRASwt synchronous non-resectable liver-limited metastases were assigned to receive chemotherapy alone (FOLFIRI or FOLFOX) or in combination with cetuximab. The ORR was 57.1% in the association arm and 29.4% in the chemotherapy only arm (p = 0.001), with a R0 resection rate of 25.7% and 7.4%, respectively (p = 0.04) [36].

The impact of panitumumab as a part of a conversion strategy has been investigated in the MetaPan phase II study, in which panitumumab was associated with a doublet chemotherapy containing capecitabine and oxaliplatin (XELOX). In patients with KRASwt tumors, the ORR was 60%, with a conversion rate of 42% of initially unresectable patients being able to undergo curative surgery [30].

Individualized approach

As we have outlined, different regimens translate into different treatment options, the choice of which has to be evaluated by taking into account each patient's baseline characteristics, previous therapies, pathological information and surgical strategy.

What do we know before starting systemic treatment?

The major baseline characteristics of the patient that influence the treatment choice are age and performance status (PS).

As a result of increasing life expectancy, the incidence of CRC in older patients is progressively rising. Whether to give treatment to this large population or not should not be based on temporal age only, but also on functional status, social situation and pathologic/pharmacologic factors [38].

A determination of the frailty by additional assessment tools routinely used by geriatricians, such as activities of daily living (ADL) [39], is mandatory and can predict which patients are more likely to develop adverse events [[40], [41]].

Several studies, mainly retrospective series, suggest that both surgical and medical treatments in this population are as safe and effective as in the younger population [[42], [43], [44]], but data on an integrated conversion strategy are lacking. The current evidence supports treatment for fit elderly patients, who can achieve similar outcomes to that of younger patients [45].

Although not routinely tested in clinical practice, some genetic alterations have been correlated to standard chemotherapy agents, both for response to treatment or development of toxicities. In particular, ERCC1 polymorphisms, thymidine phosphorylase, or thymidylate synthase expression are associated with the efficacy of oxaliplatin or 5-FU [[46], [47], [48]]. Efficacy of irinotecan treatment could be associated with topoisomerase I overexpression [[49], [50]]. As for toxicity, dihydropyrimidine dehydrogenase deficiency and UGT1A1 polymorphism have been correlated with the onset of severe, unexpected toxicity respectively to fluoropyrimidines and irinotecan [[51], [52], [53]]. More recently, the individuation of specific alterations leading to defective DNA repair has paved the way for using well-known alkylating agents, such as dacarbazine, in CRC patients [54].

Other important baseline information includes biologic characteristics of the disease, namely the mutational status of KRAS and other relevant oncogenes.

In the past few years, the KRAS mutational status has been validated as a predictive factor of response to the anti-EGFR antibodies cetuximab and panitumumab [[55], [56], [57], [58], [59]].

Additional genotyping of KRAS downstream genes could be a strategy for selecting patients eligible for anti-EGFR therapy; several retrospective analyses, preclinical models and patients' series have shown how mutations of certain markers downstream of KRAS could impact on the response to anti-EGFR MoAbs [[60], [61], [62], [63], [64]]. The resistance to cetuximab in KRAS-mutant mCRC cannot be reverted either in the presence of ADCC activation mediated by leinalidomide [[65], [66]].

In the retrospective analysis by De Roock et al., it was demonstrated that patients with mutations in one of the genes BRAF, NRAS, or PIK3CA exon 20 show a lower RR compared to wild type patients in a KRASwt population treated with cetuximab [67].

Undoubtedly, the EGFR pathway is currently one of the most relevant research topics because of its implications in both upfront selection of patients prior to targeted treatment and monitoring of secondary resistance [[63], [68], [69]]. In clinical practice, mutational status of KRAS on exon 2 has been the only predictive marker routinely tested for years, but recent analysis on large randomized trials have shown that a larger screening for mutations on KRAS exon 3 or 4, NRAS exon 2, 3, or 4, or BRAF exon 15 is required prior to using anti-EGFR MoAb therapy. Among patients with wtKRAS on exon 2, 17–31% might harbor other RAS mutations that interfere with response to targeted agents; in this population the addition of cetuximab or panitumumab in the treatment plan might have a detrimental effect. On the contrary, all-RAS wild type patients show a significant improvement in both OS and PFS. Similarly, ORR is improved in all-RAS wild type patients treated with anti-EGFR MoAb therapy, making a deeper molecular screening crucial in the context of a conversion therapy [[25], [70], [71], [72], [73], [74]].

A second issue when using anti-EGFR MoAbs is choosing the right chemotherapy complement; based on the results of the COIN and Nordic VII trials [[75], [76]] it was suggested that oxaliplatin-based regimens might not represent an optimal backbone therapy. However, preclinical data and the final results of the PRIME and OPUS trials contradict this hypothesis [[77], [78], [79]].

This discordance may be due to the different fluoropyrimidine administration rather than a negative interaction between cetuximab and oxaliplatin; although it has never been formally demonstrated, cetuximab could be more effective with infusional 5FU than with bolus 5FU alone or capecitabine [[29], [80]].

What happens during systemic treatment?

It is now established that chemotherapy may induce liver damage; in particular oxaliplatin has been linked to sinusoidal wall disruption, resulting in sinusoidal obstruction syndrome (SOS) [[81], [82], [83]]. Similarly, irinotecan can induce a type of non-alcoholic fatty liver disease known as steatohepatitis [[84], [85]].

Conversely, no specific hepatic toxicity has been linked to MoAbs [86] and, in particular, a protective role of bevacizumab against the development of SOS has been demonstrated in several publications [[87], [88], [89]].

Chemotherapy-associated liver injuries may cause bleeding during surgery or poor liver reserve which both result in increased postoperative morbidity and mortality rates [[90], [91]].

It is therefore necessary to closely monitor tumor shrinkage (for example with a TC-scan every 8 weeks) and plan the timing of the resection to coincide with completion of the minimum number of chemotherapy courses required to achieve resectability, as it has been demonstrated that prolonged chemotherapy does not improve the pathologic response but just increases the risk of hepatotoxicity [92].

Regarding response to therapy, in order to maximize the disease downsizing to facilitate resection, the choice of the drug combination regimen is critical to the success of the curative strategy. A strong relationship between tumor RR and resection rates has been demonstrated in mCRC treated with chemotherapy [93]. Furthermore, pathological analysis after systemic treatment may reveal prognostic information, such as tumor regression rate. The scoring system is based on the presence of fibrosis overgrowing on tumor cells, rather than the increase of necrosis. Patients experiencing major histological tumor regression showed an improved 3-year disease free survival (DFS) compared with those who had partial or no regression, resulting in a better 5-year OS rate. As for the chemotherapy regimen used as a

neoadjuvant systemic treatment, histological tumor regression was most common among oxaliplatin-treated patients and it was associated with a better clinical outcome [94].

One of the major concerns is related to the disappearance of metastases as a consequence of neoadjuvant therapy. It has been demonstrated that viable tumor cells persist in up to 80% of metastases after complete radiological response [[95],[96]]. This poses the surgeon in a puzzling situation; it has been suggested that in such cases liver resection should include all the sites of a tumor detected prior to systemic treatment [97].

Conclusions

We have overviewed the current evidence for mCRC treatment, focusing on the individualized approach to resectability. Tailoring the treatment strategy is now possible and, as we have shown in our review, patients presenting with CRC metastases should be evaluated for multimodal management with curative intent [22]. Clinical studies specifically designed for potentially resectable patients in the context of a conversion strategy are required; more homogeneous criteria of resectability should be therefore used across the studies. We suggest that, in the case of hepatic disease, unresectability is defined as ≥1 of the following: no possibility of upfront R0/R1 resection of all hepatic lesions, <30% estimated residual liver after resection, or disease in contact with major vessels of the remnant liver.

Drawing evidence-based conclusions about the best regimen to use is sometimes difficult; only a small number of clinical trials are specifically designed for conversion systemic treatment. Data are generally retrieved from larger phase III studies where the primary endpoint is PFS or OS and patient population often varies. In addition, data on metastasectomies available in the literature mainly regard hepatic lesions, not taking into account the recent progress that has been made in thoracic and abdominal surgery [[98], [99], [100]].

The introduction of targeted agents has led to the definition of new paradigms in clinical oncology. The final goal will be to maximize the therapeutic index of novel agents, while at the same time providing the actual translation of individualized therapy into the clinical setting.

Even though the identification of genetic markers may drive the treatment strategy and improve outcomes, the binary correlation between a mutated cancer gene and the response to a targeted therapy is proving more difficult than expected. This may be due to the intratumor heterogeneity [101] and the complexity of the signaling pathways in an individual cancer. The importance of selecting different molecular predictive markers prior to treatment is progressively emerging [70].

At the same time, it must be taken into account that a large percentage of patients do not express any "druggable" alteration. This might be due to different factors; absence of "driving" genetic alterations, activation of distinct pathways at the same time or absence of efficacy-proven targeted drugs. Maximizing the impact of systemic treatment in this population is furthermore challenging as it involves the field of early drug development, hitting new druggable pathways or combining targeted agents.

The preferred choice of MoAb for a conversion therapy remains debatable. A direct comparison between cetuximab and bevacizumab in association with FOLFIRI, in the multicenter, randomized phase III FIRE-3 trial showed a 62% ORR in FOLFIRI-cetuximab arm vs. 57% in FOLFIRI-bevacizumab arm (p = 0.183). No difference in PFS was found (10.3 vs. 10.4 months for cetuximab and bevacizumab arm, respectively). The difference in OS, however, reached a statistically significant value in favor of cetuximab (28.8 vs. 25.0

months; p = 0.0164) [28]. Similarly, the comparison of bevacizumab or panitumumab with mFOLFOX6 in a phase II randomized trial showed similar ORR (54% for bevacizumab and 58% for panitumumab), PFS (10.1 vs. 10.9 months) and OS (25.4 months vs. not yet reached) [34].

These results regarding OS, especially in the all-RAS wild type population, seem to favor a frontline treatment with anti-EGFR MoAbs, but a clearer evidence on ORR and resection rate in potentially resectable patients is still needed; results from the CALGB/SWOG 80405 trial are pending, and randomized trials or ad hoc analysis in the conversion setting might finally answer the question whether the addition of a specific MoAb can improve the resection rate in all-RAS wild type population.

For RAS or BRAF mutated patients, triplet chemotherapy and combinations with bevacizumab represent two rationale alternatives on the basis of high response rates and tumor shrinkage [102], but their efficacy in conversion setting has not yet been demonstrated in specifically designed studies.

Whether combination of triplets and targeted agents should be considered another step forward, requires further confirmation; in our opinion this field of research might be particularly promising in the setting of conversion therapy.

Conflict of interest

Authors declare that they have no conflict of interest.

Reviewers

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Acknowledgements

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