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REVIEW

Primary tumor resection in colorectal cancer with unresectable synchronous metastases: A review

Louis de Mestier, Gilles Manceau, Cindy Neuzillet, Jean Baptiste Bachet, Jean Philippe Spano, Reza Kianmanesh, Jean Christophe Vaillant, Olivier Bouché, Laurent Hannoun, Mehdi Karoui

Louis de Mestier, Olivier Bouché, Department of Gastroenterology and Digestive Oncology, Robert-Debré University Hospital, 51100 Reims, France
Gilles Manceau, Jean Christophe Vaillant, Laurent Hannoun, Mehdi Karoui, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Department of Digestive and Hepato-Pancreato-Biliary Surgery, University Institute of Cancerology (Paris VI), Pierre and Marie Curie University, 75013 Paris, France
Cindy Neuzillet, Assistance Publique-Hôpitaux de Paris, Department of Gastroenterology and Pancreatology, Beaujon University Hospital, 92110 Clichy, France
Jean Baptiste Bachet, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Department of Gastroenterology, University Institute of Cancerology (Paris VI), Pierre and Marie Curie University, 75013 Paris, France
Jean Philippe Spano, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Department of Medical Oncology, University Institute of Cancerology (Paris VI), Pierre and Marie Curie University, 75013 Paris, France
Reza Kianmanesh, Department of Digestive and Endocrine Surgery, Robert-Debré University Hospital, 51100 Reims, France
Author contributions: de Mestier L, Manceau G, Neuzillet C, Bachet JB, Spano JP, Kianmanesh R, Vaillant JC, Bouché O, Hannoun L and Karoui M designed research; de Mestier L, Manceau G, Karoui M performed research; de Mestier L, Manceau G and Karoui M analyzed data; de Mestier L, Manceau G, Neuzillet C, Bachet JB, Spano JP, Kianmanesh R, Vaillant JC, Bouché O, Hannoun L and Karoui M wrote the paper.
Correspondence to: Mehdi Karoui, MD, PhD, Professor of Surgery, Assistance Publique-Hôpitaux de Paris, Pitié Salpêtrière University Hospital, Department of Digestive and Hepato-Pancreato-Biliary Surgery, University Institute of Cancerology (Paris VI), Pierre and Marie Curie University, 47-83 Boulevard de l'Hôpital, 75013 Paris, France. mehdi.karoui@psl.aphp.fr
Telephone: +33-1-42175612 Fax: +33-1-42175613
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Abstract

At the time of diagnosis, 25% of patients with colorectal cancer (CRC) present with synchronous metastases, which are unresectable in the majority of patients. Whether primary tumor resection (PTR) followed by chemotherapy or immediate chemotherapy without PTR is the best therapeutic option in patients with asymptomatic CRC and unresectable metastases is a major issue, although unanswered to date. The aim of this study was to review all published data on whether PTR should be performed in patients with CRC and unresectable synchronous metastases. All aspects of the management of CRC were taken into account, especially prognostic factors in patients with CRC and unresectable metastases. The impact of PTR on survival and quality of life were reviewed, in addition to the characteristics of patients that could benefit from PTR and the possible underlying mechanisms. The risks of both approaches are reported. As no randomized study has been performed to date, we finally discussed how a therapeutic strategy's trial should be designed to provide answer to this issue.

Key words: Colorectal cancer; Colorectal surgery; Chemotherapy; Colorectal primary tumor; Survival; Liver metastases

Core tip: The present review aimed to analyze all published data on whether primary tumor resection should be performed before chemotherapy administration in patients with colorectal cancer and unresectable synchronous metastases.

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INTRODUCTION

With nearly 150000 new cases in the United States annually (about 1 million in developed countries) and 55000 annual deaths (about 500000 in developed countries), colorectal cancer (CRC) stands as the second leading cause of cancer death in Western countries and a significant public health issue[1]. In approximately 20% of patients, distant metastases are already present at the time of diagnosis[2]. The liver is the most common metastatic site. Surgery plays an important role in the treatment of patients with limited metastatic disease with 20%-50% rates of cure and long-term survival after complete R0 resection[3]. However, for the majority (75%-90%) of these CRC patients with synchronous liver metastases (SLM), there are no curative options, but a significant benefit in median overall survival (OS) and quality of life can be achieved with palliative systemic treatment, namely effective chemotherapy regimens and targeted biotherapies[4,5].

Patients with CRC and unresectable SLM may present with a variable degree of symptoms of their primary tumor. The indication of palliative primary tumor resection (PTR) prior to the initiation of systemic treatment is obvious in patients with primary tumor-related symptoms or complications (obstruction, bleeding, or perforation). However, in asymptomatic CRC patients with unresectable SLM, the indication of PTR as initial management remains questionable and its effect on survival and quality of life is uncertain. No randomized trial has answered to these questions to date[6-13].

Historically, many surgeons have advocated PTR, mainly to avoid potential related complications such as bleeding, perforation or obstruction and because it allows precise tumor staging[14,15]. However, during the past decade, several highly active systemic agents have become available for the treatment of metastatic CRC patients. These agents have increased the median survival duration from 9 to 12 mo with 5-fluorouracil alone, to 24 mo with the addition of modern cytotoxic and targeted agents[16-20]. Owing to the increased efficacy of chemotherapy on metastatic CRC as well as on primary tumor[21], complications from unresected primary tumor have become relatively infrequent. Therefore, there is a tendency among surgeons not to perform PTR in case of unresectable metastases. The possible influence of PTR on survival of patients with CRC and unresectable SLM has never been assessed properly. It has been suggested that PTR, in the setting of unresectable metastatic disease, was related to prolonged survival on multivariate analysis in the majority of these series[6-10,12,13,22]. Nevertheless, most studies reporting an association between PTR and prolonged survival have been limited by numerous selection biases. In addition, whether these two strategies impact patient's quality of life has never been evaluated. Finally, the relative low post-operative morbidity rates reported after laparoscopic resection in stage Ⅳ CRC[23-25] and the progress in perioperative management of these patients, have reinforced the debate between the two strategies (PTR *vs* no PTR). While waiting for a randomized study, the objective of the present work was to review the state of the art on the management of CRC patients with unresectable synchronous metastases, with particular focus on PTR.

TREATMENT OF METASTATIC COLORECTAL CANCER

When metastases of CRC patients are restricted to the liver, possible curative treatment can be obtained by surgical resection of the metastases. Patients with oligometastases restricted to the lungs may also be candidates for surgical resection. Complete surgical resection of metastatic lesions substantially improves overall survival rates to around 35%-60% in selected patients[3]. Even extra-hepatic disease is no longer a contraindication for surgery in selected patients[26]. Hyperthermic intraperitoneal chemotherapy is a promising treatment in selected patients with limited peritoneal carcinomatosis and long term survival can be achieved[27]. In all other cases, CRC patients with unresectable metastases are treated with systemic combination chemotherapy regimens. Most common combinations are oxaliplatin or irinotecan in addition to a fluoropyrimidine (capecitabine or 5-fluorouracil). Since the last decade, targeted biotherapies have been possibly administered in addition, such as antiangiogenic therapy (*i.e.*, bevacizumab) and anti-epidermal growth factor receptor antibodies *(i.e.*, panitumumab and cetuximab) in the setting of *KRAS* wild-type tumors. These systemic chemotherapeutic combinations have raised response rates to 40%-75% resulting in a median overall survival rate of approximately 24 mo[5,19,28,29]. With current chemotherapy regimens, around 20% of the tumors initially judged unresectable have been converted to resectable, leading to secondary curative surgery and similar prognosis than in patients who underwent surgery for initially resectable liver metastases[3,30].

IMPACT OF PRIMARY TUMOR RESECTION ON THE SURVIVAL OF PATIENTS WITH COLORECTAL CANCER AND UNRESECTABLE SYNCHRONOUS LIVER METASTASES

In patients with asymptomatic primary tumor and unresectable SLM, PTR prior to the initiation of systemic treatment is questioned. Its effects on survival and quality of life are uncertain[6-18,31,32]. No randomized control trial has been conducted to date.

Several studies have been performed to analyze the survival in patients with unresectable stage Ⅳ CRC un-

Table 1 Median survival (mo) in patients with unresectable metastatic colorectal cancer, according to whether primary tumor resection was performed or not

Ref.	Study period	Resection/ No resection	No.of patients	OS (mo)	*P* value
Scoggins *et al*[82]	1985-1997	Resection	66	14.5	0.59
		No resection	23	16.6	
Tebbutt *et al*[34]	1990-1999	Resection	280	14	0.08
		No resection	82	8.2	
Ruo *et al*[44]	1996-1999	Resection	127	16	< 0.001
		No resection	103	9	
Michel *et al*[90]	1996-1999	Resection	31	21	0.718
		No resection	23	14	
Law *et al*[35]	1996-1999	Resection	150	7	< 0.001
		No resection	30	3	
Benoist *et al*[79]	1997-2002	Resection	32	23	NS
		No resection	27	22	
Stelzner *et al*[45]	1995-2001	Resection	128	11.4	< 0.0001
		No resection	58	4.6	
Konyalian *et al*[36]	1991-2002	Resection	62	13	< 0.0001
		No resection	47	5	
Costi *et al*[91]	1994-2003	Resection	83	9	< 0.001
		No resection	47	4	
Yun *et al*[37]	1994-2004	Resection	283	15.3	< 0.001
		No resection	93	5.3	
Kaufman *et al*[92]	1998-2003	Resection	115	22	< 0.0001
		No resection	69	3	
Galizia *et al*[38]	1995-2005	Resection	42	15.2	0.03
		No resection	23	12.3	
Evans *et al*[70]	1999-2006	Resection	45	11	< 0.0001
		No resection	57	2	
Bajwa *et al*[39]	1999-2005	Resection	32	14	0.005
		No resection	35	6	
Mik *et al*[40]	1996-2000	Resection	52	21	NS
		No resection	82	14	
Frago *et al*[93]	2004-2008	Resection	12	23.7	0.008
		No resection	43	4.4	
Aslam *et al*[41]	1998-2007	Resection	366	14.5	< 0.005
		No resection	281	5.83	
Chan *et al*[11]	2000-2002	Resection	286	14	< 0.001
		No resection	125	6	
Seo *et al*[94]	2001-2008	Resection	114	22	0.076
		No resection	83	14	
Karoui *et al*[33]	1998-2007	Resection	128	30.7	0.031
		No resection	85	21.9	
Ferrand *et al*[22]	1997-2001	Resection	156	16.3	< 0.0001
		No resection	60	9.5	

OS: Overall survival.

dergoing PTR, in comparison with those who did not (Table 1). All were non-randomized and most were single-center and retrospective. In addition, the major drawback of these studies is that patients with a better World Health Organization performance status (WHO-PS) and better prognosis at baseline (less metastatic sites involved) were more likely to undergo surgery. Conversely, patients with extensive disease were more likely to be offered chemotherapy rather than surgery thus standing as a major selection bias. Similarly, only patients with good WHO-PS were able to tolerate a complete course of potentially toxic chemotherapeutic agents such as irinotecan and oxaliplatin. Another limitation is that reported data on the use of systemic therapy are scarce, which hardens the assessment of the influence of PTR on outcome. Despite these limitations, the median OS was improved in resected patients in the vast majority of studies.

Our group recently reported a 10-year retrospective experience of the management of metastatic colonic cancer in chemotherapy-eligible patients, managed in 6 Parisian university hospitals[33]. The primary aim of this study was to compare outcomes, including survival, in 208 patients with unresectable distant metastases undergoing either PTR (n = 85) or systemic chemotherapy (n = 123) as their initial treatment. Most patients had not received targeted therapy as first-line treatment. Median OS was nearly 9 mo longer after PTR than after initial systemic chemotherapy (30.7 mo *vs* 21.9 mo, adjusted HR= 0.56; P = 0.031). In this series, the 2 groups were different with respect to baseline carcinoembryonic antigen (CEA) level, which was lower in the colectomy group (P = 0.008), suggesting a lower disease burden[33]. Despite similar rates of chemotherapy administration, the secondary curative resection rate was higher in the PTR group than in patients treated with initial chemotherapy (32.9% *vs* 20.3%; P = 0.04), suggesting a lower metastatic burden and other potential unmeasured differences contributing to a greater response to chemotherapy. In an effort to take into account these differences, a propensity score was performed and used for adjustment. On multivariate analysis, first-intent PTR, secondary curative resection, well-differentiated primary tumor, liver-only metastases and addition of targeted therapy were independently associated with survival. After adjusting on the propensity score quartiles, as well as for the quantitative value of this score, these five factors were still independently associated with survival[33].

A recent meta-analysis of 8 retrospective comparative studies including 1062 patients has reported an improvement in the survival of those with palliative PTR, with an estimated median gain of 6 mo (standardized HR = 0.55; 95%CI: 0.29-0.82; P < 0.001)[8]. The initial heterogeneity between the studies was amended after excluding one study[34], in which survival was not the primary endpoint. The authors also reported that PTR was not associated with increased secondary resectability of metastases following chemotherapy, in comparison with patients treated with chemotherapy alone (HR = 0.85; 95%CI: 0.4-1.8, P = 0.66)[8].

Venderbosch *et al*[12] performed a retrospective analysis of two phase Ⅲ studies (CAIRO and CAIRO2), investigating the prognostic and predictive value of PTR in patients with synchronous stage Ⅳ CRC treated with systemic therapy. In the CAIRO study, 258 patients underwent PTR (*vs* 141 who did not) and showed increased median OS (16.7 mo *vs* 11.4 mo, respectively; HR = 0.61; P < 0.0001) and progression-free survival (PFS) (6.7 mo *vs* 5.9 mo, respectively; HR = 0.74; P = 0.004). Similarly, in the CAIRO2 study, 289 patients underwent PTR (*vs* 159 who did not) and showed increased median OS (20.7 *vs* 13.4 mo; HR = 0.65; P < 0.0001) and PFS (10.5 mo *vs* 7.8 mo; HR = 0.78; P = 0.014)[12]. A major limitation of these results consisted in the fact that the decision of PTR was made prior to study inclusion. Besides, no information about the reasons for non-resection were provided, such as absence of symptoms, unresectability of the primary

Table 2 Prognostic factors associated with overall survival in patients with unresectable metastatic colorectal cancer, according to whether primary tumor resection was performed or not

Ref.	Resection/No resection	No. of patients	OS (mo)	*P* value	PTR on multivariate analysis [95%CI]	Other independent prognostic factors
Tebbutt *et al*[34]	Resection	280	14	0.08	No	WHO-PS < 2, no peritoneal dissemination, low phosphatase alkaline and serum albumin levels
	No resection	82	8.2			
Law *et al*[35]	Resection	150	7	< 0.001	OR = 0.42 (0.27–0.66)[1]	Unilobar LM involvement, no ascites, no chemotherapy
	No resection	30	3		*P* < 0.001	
Stelzner *et al*[45]	Resection	128	11.4	< 0.0001	HR = 0.50 (0.27–0.90)	No chemotherapy, ASA score < 3, WHO-PS < 2, CEA level, age < 75 yr, extent of metastases, extent of primary tumor
	No resection	58	4.6		*P* = 0.021[2]	
Konyalian *et al*[36]	Resection	62	13	< 0.0001	HR = 0.3 (0.2–0.6)	Liver involvement < 50%
	No resection	47	5		*P* < 0.0001[3]	
Yun *et al*[37]	Resection	283	15.3	< 0.001	HR = 0.53 (0.38–0.73)	Metastatic site ⩽ 1, high CEA level, chemotherapy, well-differentiated primary tumor
	No resection	93	5.3		*P* < 0.001	
Galizia *et al*[38]	Resection	42	15.2	0.03	OR = 3.91 (2.83-4.99)	WHO-PS < 2, liver involvement < 50%
	No resection	23	12.3		0.26 (0.20-0.35)[1] *P* = 0.001	
Bajwa *et al*[39]	Resection	32	14	0.005	OR = 0.26 (0.13-0.52)	Left sided primary tumor, unique primary tumor
	No resection	35	6		*P* = 0.0001	
Mik *et al*[40]	Resection	52	21	NS	HR = 0.58 (0.36–0.82)[1]	Unilobar LM involvement
	No resection	82	14		*P* = 0.004	
Aslam *et al*[41]	Resection	366	14.5	< 0.005	*P* < 0.001	Age < 80 yr, non-locally advanced primary tumor, N + stage
	No resection	281	5.83			
Karoui *et al*[33]	Resection	128	30.7	0.031	HR = 0.56 (0.38–0.83)[1]	Secondary curative resection, well-differentiated primary tumor, anti-VEGF treatment, no extra-hepatic metastases
	No resection	85	21.9	-	*P* = 0.004	
Platell *et al*[83]	Resection	243	-		HR = 0.51 (0.37–0.69)	Chemotherapy, radiotherapy, ASA score < 3
	No resection	70	-		*P* = 0.0001	
Venderbosch *et al*[12]	Resection	286	14	< 0.001	HR = 0.73 (0.58-0.93)	-
	No resection	125	6		*P* = 0.01	
Ferrand *et al*[22]	Resection	156	16.3	< 0.0001	HR = 0.42 (0.30-0.60)	WHO-PS < 2, distal colon or rectal primary tumor, one metastatic site and alkaline phosphatase ⩽ 300 UI/L
					P < 0.0001	
	No resection	60	9.5			

[1]For readability of the Table, some ORs and HRs have been recalculated with " No resection" as reference for the multivariate analysis of survival; [2]excluding postoperative mortality and complicated primary tumor; [3]PTR was independently associated with increased survival probability, while adjusting on patient's age, sex and degree of hepatic tumor involvement. OS: Overall survival; PTR: Primary tumor resection; OR: Odds ratio; HR: Hazard ratio; LM: Liver metastases; ASA: American society of anesthesiology; CEA: Carcinoembryonic antigen; VEGF: Vascular-endothelial growth factor; WHO-PS: World health organization performance status; NS: Not significant.

tumor, poor patient condition and/or symptomatic metastases requiring rapid initiation of systemic treatment. Obviously, many differences were likely to stand between patients undergoing PTR or not. However, on multivariate analysis, PTR remained a significant prognostic factor in the CAIRO2 study and in the subgroup of patients with one metastatic site in the CAIRO study[12].

Finaly, Ferrand *et al*[22] recently performed an analysis of 260 patients included in the Fédération Francophone de Cancérologie Digestive 9601 phase Ⅲ trial, which compared different first-line single-agent chemotherapy regimens in patients with stage Ⅳ CRC. Two-year OS and 6-mo PFS were significantly better in the resection group than in the non-resection group (24% *vs* 10%; *P* < 0.0001 and 38% *vs* 22%; *P* = 0.001, respectively). The gain of OS was 6.8 mo. These results remained significant even after exclusion of the 49 patients with rectal cancer. In multivariate analysis, PTR was the most significant prognostic factor (HR = 0.42; 95%CI: 0.30-0.60, *P* < 0.0001). In this study, 4 factors were associated with a decreased survival: poor WHO-PS, multiple metastatic sites, proximal colonic primary tumor and high baseline alkaline phosphatase level.

WHICH PATIENTS WITH COLORECTAL CANCER AND UNRESECTABLE SYNCHRONOUS LIVER METASTASES ARE LIKELY TO BENEFIT FROM PRIMARY TUMOR RESECTION?

Some comparative studies conducted multivariate analysis to determine which clinical, tumor and therapy variables were associated with survival between patients managed by primary surgery or immediate chemotherapy[10] (Table 2). In addition to PTR, several factors were found to have independent prognostic influence: age, American society of anesthesiology (ASA) score, WHO-PS, preoperative CEA levels, primary tumor location, size and differentiation, extent of metastatic liver spread, peritoneal dissemination and extra-hepatic metastases. Other independent factors have been less frequently reported, such as serum albumin, alkaline phosphatase levels, lymph node involvement, ascites, number of metastatic sites and the administration of targeted therapy. Some works also emphasized that tumor burden (primary tumor and/or metastatic

Table 3 Prognostic factors after primary tumor resection on multivariate analyzes

Ref.	Metastatic spread	No. of patients	Prognostic factors or predictive factors of postoperative morbimortality
Rosen *et al*[43]	Liver, Peritoneum	125	Age < 65 yr, limited LM, no peritoneal carcinomatosis
Ruo *et al*[44]	Liver, peritoneum, retroperitoneal lymph nodes, lung, bone, brain	123	Liver involvement < 25%
Stelzner *et al*[45]	Mainly liver	186	WHO-PS, ASA grade, low CEA level, metastatic load, chemotherapy
Vibert *et al*[47]	Liver	80	Serum AST level < 50 IU/l, age < 75 yr
Yun *et al*[37]	Liver, peritoneum, lung	503	CEA level, well-differentiated primary tumor, chemotherapy
Kleespies *et al*[46]	Mainly liver, lung, peritoneum	233	Liver involvement < 50%, chemotherapy, pT4 and/or N+ stage
Costi *et al*[48]	Mainly liver, peritoneum	71	Age < 80 yr, nodal stage
Stillwell *et al*[31]	Liver and extra-hepatic	379	Nodal stage < N2, well-differentiated primary tumor, no postoperative complications, no apical lymph-node

LM: Liver metastases; ASA: American society of anesthesiology; CEA: Carcinoembryonic antigen; WHO-PS: World health organization performance status.

disease) was significantly related to survival[22,33-42]. Bilobar liver metastases were associated with decreased survival compared to unilobar location, the risk of cancer-related death being five-fold increase in case of > 50% liver involvement[35,36,38,40]. Similarly, peritoneal and omental metastases are significantly related to poorer survival[34].

Furthermore, several studies reported multivariate analysis of predictive factors affecting outcome after PTR in patients with CRC and unresectable SLM. The main factors influencing outcome were the extent of liver disease[42-46], age[43,47,48] and tumor differentiation[31,37] (Table 3).

The results of the study by Vibert *et al*[47] suggested that patients older than 70 years with elevated aspartate aminotransferase enzymes may not benefit from palliative PTR and could be offered chemotherapy if suitable. A retrospective review of 503 palliative PTR found that predictors of survival included serum CEA level, degree of differentiation of the tumor, successful PTR and the use of chemotherapy[37]. In another study, age > 65, the presence of carcinomatosis and extensive bilobar liver involvement were not only associated with decreased survival after PTR, but with increased morbidity and mortality as well[43]. Kuo *et al*[49] suggested that patients older than 65 with multiple-site metastases, intestinal obstruction, preoperative CEA levels > 500 ng/mL, lactate dehydrogenase > 350 units/L, hemoglobin < 10 g/dL, or liver tumor burden > 25% exhibited worse survival following surgery than those without.

To summarize, most of studies suggested that liver burden > 50% and extra-hepatic metastatic disease (peritoneal carcinomatosis, lung metastases) were poor prognostic factors in patients with CRC and unresectable SLM, as well as advanced age and poor WHO-PS. Interestingly, this appears to have remained unchanged with time despite the advances in the surgery and systemic therapy. Thus, patient selection is a critical issue, and the decision for PTR should take into account these prognostic factors.

UNDERLYING HYPOTHESES FOR INCREASED SURVIVAL IN PATIENTS UNDERGOING PTR

Reasons why PTR is associated with better outcomes in patients with CRC and unresectable metastases are still unclear. The improvement in survival following PTR may be attributed to a better response to chemotherapy after reduction of tumor burden. This has been demonstrated by the proven benefit of resecting primary renal and ovarian tumors in the presence of metastatic disease[50,51]. Survival of resected patients might also be improved because they are less likely to develop obstruction and perforation, complications known to carry heavy operative mortality and morbidity[8]. Besides, surgical removal of primary tumor may restore immunocompetence, even at a metastatic stage, as shown in a murine model xenografted with 4T1 mammary carcinoma[52].

It has been suggested that the interaction between primary tumor and target organs of metastasis dictates the progression from micro- to macrometastases[53]. Indeed, the primary tumor may induce, in these distant organs, a prosperous environment to enhance the growth of metastatic deposit (seed and soil theory). Vascular endothelial growth factor receptor 2 (VEGFR-2) expressing circulating tumor cells settle in the pre-metastatic niches, previously colonized by hematopoietic cells expressing VEGFR-1[54]. The recent study by van der Wal *et al*[55] suggested that PTR could prevent the liver parenchyma from soiling from micrometastases. Indeed, the authors demonstrated that the expression levels of angiogenetic markers (CD31, VEGF-A, VEGFR-1, VEGFR-2, Placental Growth Factor, Hypoxia-induced Factor 1 alpha, Angiopoietin-2 and its receptor Tie-2, all assessed using reverse transcription-polymerase chain reaction) were higher in the liver parenchyma adjacent to metastases, both in patients with simultaneous resection of both their primary tumor and liver metastases, and in those who underwent metastases removal several months after PTR. Moreover, the simultaneous resection group showed the highest Ang-2/Ang-1 (proangiogenic) ratio both in the metastases and the adjacent liver. These results suggested that in the presence of the primary tumor, the liver parenchyma adjacent to metastases provided an angiogenic prosperous soil for metastatic tumor growth and may explain the association of PTR with improved survival[55]. These results are also in concordance with the prognostic role of anti-VEGF based treatment we found on multivariate analysis in our series[33].

In contrast, several studies based on PET-scan and histology showed an increased growth of liver metastases following PTR, as determined by an increased vascular density, proliferation rate, and metabolic growth rate[56-59]. These data suggest that the outgrowth of metastatic disease may, at least partly, be downregulated by the primary tumor, notably by inhibiting metastatic angiogenesis. In mouse models, pulmonary metastases showed rapid progression after PTR, which was considered to be the result of depletion of the antiangiogenic compound angiostatin produced by the primary tumor[53,56,60]. After PTR, antiangiogenic effects disappear, and metastases undergo an "angiogenic switch", leading to angiogenesis and enhanced tumor growth[60]. In addition, major surgery induces a transient immunodepression which may promote tumor growth[61,62]. Romano *et al*[63] reported that 29% of CRC patients had lymphocytopenia at baseline. In comparison, 14 d after surgery, values below normal range for total lymphocyte count and helper T-cells were found in 44% and 53% of cases, respectively. Recovery of postoperative surgery-related lymphocytopenia occurred late only in patients with normal count at baseline. In a rat model, perioperative restoration of lymphocyte proliferation levels either by levamisole or maleic anhydride-divinyl ether-2 resulted in fewer hepatic metastases, suggesting the critical role of immunomodulation in the development of metastases[64,65]. Notably, perioperative blood transfusions have been shown to exert an immunosuppressive effect on patients with CRC and are independently associated with a poor prognosis[66,67].

However, these pro-tumoral effects seem to be counterbalanced by previously described anti-tumoral effects of PTR, as most studies have reported an association between PTR an improved outcome. Overall, it seems ethically relevant to perform a clinical trial comparing PTR to conservative strategy, as data remains controversial regarding PTR consequences on tumor evolution. Indeed, influence of primary tumor on angiogenesis of metastases are based on experimental studies, which does not necessarily translate clinically into a modification of patient survival. Studies that showed an advantage of PTR had such selection bias that interpretation of their findings are difficult, even with the use of multivariate analyzes or propensity scores. Definitive response regarding the interest of PTR in stage Ⅳ CRC patients could only be obtained with a randomized trial with selective inclusion criteria and comparable arms.

IMPACT OF PRIMARY TUMOR RESECTION ON QUALITY OF LIFE OF PATIENTS WITH COLORECTAL CANCER AND UNRESECTABLE SYNCHRONOUS LIVER METASTASES

The effect of PTR and chemotherapy on quality of life has never been specifically evaluated. In the palliative care setting, determining the effect of PTR on quality of life would help clinicians and patients deciding the most adapted primary strategy. Primary-related symptoms or complications, postoperative morbidity following PTR (either electively or for complications), total length of hospital stay and tolerability of chemotherapy (according to the presence or absence of the primary tumor) may all contribute to impact quality of life. They should thus stand as secondary endpoints in a future prospective randomized study evaluating the impact of PTR in CRC patients with unresectable synchronous metastases. Quality of life could be assessed in both arms with the use of validated questionnaires such as the european organization for research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) and EORTC-CR29, at baseline and after initiation of treatment (surgery or chemotherapy) with longitudinal follow-up.

WHAT ARE THE RISKS OF UNRESECTED PRIMARY TUMOR-RELATED COMPLICATIONS UNDER CHEMOTHERAPY?

PTR has been traditionally advocated in the setting of metastatic CRC, to prevent symptoms and complications linked to primary tumor, such as obstruction, perforation or bleeding. Emergency surgery is associated with high morbidity and even mortality[45,68-70]. The risk of local complications related to tumor left in situ, during initial chemotherapy, varied from 8.5% to 30% and was dominated by the risk of obstruction (6%-29%) (Table 4). These results require cautious interpretation, as they came from old retrospective series that involved few patients supported for long periods with heterogeneous chemotherapy regimens. In addition, many of these series have included patients with primary tumor-related symptoms or complications at initial presentation[33,44,71].

With recent advances in systemic chemotherapy, the risks and benefits of immediate or deferred surgical strategy have changed. In contrast to the response rates of approximately 15% to 5-fluorouracil, combinations with modern chemotherapy regimens, such as infusional 5-fluorouracil/leucovorin with oxaliplatin or irinotecan, have yielded response rates of 50% and disease control rates of 85% in prospective clinical trials[72,73]. Furthermore, the addition of the targeted agents bevacizumab or cetuximab to the above combinations has provided clinically significant improvement in response rates[5,28,29,74]. In the setting of these effective chemotherapy regimens, the risk of primary tumor-related complications and the need of subsequent urgent intervention are low, less than 15% in most series (Table 4).

In series in which patients were mainly treated with effective chemotherapy (oxaliplatin, irinotecan, targeted agents) and had asymptomatic or uncomplicated primary tumor at presentation, the risk of complications was inferior to 10%, which can be explained by the significant tumor response to chemotherapy[21,75,76]. In addition, the risk of emergency colectomy for complications varies from 2% to 29%, with a rate of less than 7% in the two

Table 4 Complications related to in situ tumor in patients with unresectable stage IV colorectal cancer treated with chemotherapy as initial management *n* (%)

Ref.	No. of patients	Primary tumor-related complications (%)	Type of complication during chemotherapy			Surgery required for complication (%)
			Obstruction	Bleeding	Perforation	
Scoggins *et al*[82]	23	9	2 (9)	0	0	9
Sarela *et al*[71]	24	29	4 (17)	0	0	21
Ruo *et al*[44]	103	29	30 (29)	0	0	29
Tebbut *et al*[34]	82	23	11 (13)	3 (4%)	5 (6)	10
Michel *et al*[90]	23	22	5 (22)	0	0	22
Benoist *et al*[79]	27	15	4 (15)	0	0	15
Muratore *et al*[75]	35	8.5	2 (6)	1 (3%)	0	3
Galizia *et al*[38]	23	30	4 (17)	1 (4%)	2 (9)	17
Evans *et al*[70]	52	23	3 (6)	9 (17%)	0	2
Poultsides *et al*[76]	233	11	18 (8)	0	5 (2)	7
Karoui *et al*[33]	123	19	21 (17)	0	2 (2)	12
McCahill *et al*[77]	86	16	10 (12)	0	1 (1)	12

most recent series. In a series reporting 233 consecutive patients treated with primary chemotherapy, 26 (11%) patients developed a complication related to the primary tumor: colonic obstruction in 18 cases (9 effectively treated with a colonic stent), perforation in 5 cases, and pelvic pain in 3 patients with rectal cancer[76]. Among the 26 patients with a complication, only 16 (7%) required an intervention. In this series, no factor was correlated with the risk of primary tumor-related complication requiring an intervention under chemotherapy.

Lastly, in a phase Ⅱ trial, McCahill *et al*[77] recently reported a major morbidity rate of 16.3% (14 patients) in 86 patients with an intact primary tumor, receiving a chemotherapy by FOLFOX and bevacizumab. Primary tumor-related complications occurred in the first 12 mo following inclusion in 83.3% of cases. It consisted in 10 surgical interventions for primary tumor-related symptoms and two deaths attributed to complications of the intact primary. Among these 10 surgeries, indications were colonic obstruction in eight, perforation in one and abdominal pain in one. Six interventions were performed in emergency, three implicated performing definitive stoma and one postoperative death occurred. Four more patients had primary-related-complications, including two cases of bowel obstruction, which were managed without surgery, accounting for minor morbidity. In balance, 27 (31.4%) patients suffered from chemotherapy-related events and eight patients underwent a surgical resection with curative intent[77].

Although the expected risk is low, primary tumor-related complications may require urgent colonic stenting, or surgery with stoma creation, and may delay or even preclude chemotherapy administration. These risks should be clearly explained to patients before choosing between first-intention PTR or chemotherapy; and close follow-up performed to minimize their eventual proper consequences.

IS CHEMOTHERAPY-RELATED TOXICITY INCREASED IN THE PRESENCE OF THE PRIMARY TUMOR?

No specific studies have explored whether the presence or absence of the primary tumor could influence chemotherapy tolerance and safety. In the EORTC phase Ⅲ study[78], comparing perioperative FOLFOX chemotherapy with surgery alone, in patients with initially resectable liver metastases (≤ 4 metastases), no increased toxicity was reported in patients (34%) who had the primary tumor in place at the time of randomization. In several retrospective studies, no difference in chemotherapy-related toxicity was reported, regardless of whether the PT was in place or not[6,39,79].

Bevacizumab has been associated with a 1%-2% gastrointestinal perforation in prospective clinical trials[17,80]. Most bevacizumab-related perforations were observed in the first 3 mo of treatment, especially within the first month. It may occur throughout the entire gastrointestinal tract, including the site of the primary tumor. In the study reported by Poultsides *et al*[76] 48% of the patients received bevacizumab. Only two of the five perforations observed (all at the site of the primary tumor) occurred during bevacizumab therapy and one patient experienced perforation 6 mo after the last administration of bevacizumab, whereas two had never received it. Although the small number of patients who developed this complication may have precluded definitive conclusions, bevacizumab have not appeared to significantly increase the rate of perforation. Our group has reported similar results in a retrospective multicentric study[33]. In a recent study, among 86 patients receiving FOLFOX + bevacizumab without PTR, 23 (27%) had serious adverse events, including 4 (5%) chemotherapy-related deaths and 6 life-threatening toxicities[77]. Although not reported as serious adverse events but as primary tumor-related major morbidities, two patients had a bowel perforation, which was likely to be facilitated by bevacizumab.

For patients with *KRAS* wild-type tumor, anti-EGFR antibodies are also a possibility, although no study has yet examined the effect of these antibodies in metastatic CRC patients with the primary tumor in place[5]. Accordingly, in the particular case of colon cancer with unresectable SLM and a primary tumor in place, the literature does not currently justify a strategy different from that for CRC in general[81].

Table 5 Postoperative outcome after primary tumor resection in patients with unresectable stage IV colorectal cancer

Ref.	Study period	No. of patients	Mortality (%)	Morbidity (%)
Scoggins *et al*[82]	1985-1997	66	5	30
Rosen *et al*[43]	1984-1998	120	6	22.5
Tebbutt *et al*[34]	1990-1999	280	NM	13
Ruo *et al*[44]	1996-1999	127	2	21
Michel *et al*[90]	1996-1999	31	0	NM
Benoist *et al*[79]	1997-2002	32	0	19
Stelzner *et al*[45]	1995-2001	128	11.7	-
Galizia *et al*[38]	1995-2005	42	0	21
Evans *et al*[70]	1999-2006	45	16	NM
Bajwa *et al*[39]	1999-2005	32	3	22
Kleespies *et al*[46]	1996-2002	233	4.7	46
Mik *et al*[40]	1996-2000	52	7.7	40
Costi *et al*[48]	1994-2003	71	8.5	24
Stillwell *et al*[31]	1984-2004	379	9.2	48.3

NM: Not mentioned.

Overall, no data suggest that the presence of the primary tumor increases the toxicity of chemotherapy. Chemotherapy modalities, combined or not with targeted agents, should be the same as in the metachronous setting.

WHAT IS THE RISK OF COMPLICATIONS AFTER PALLIATIVE PRIMARY TUMOR RESECTION IN THE METASTATIC SETTING?

Several studies suggested that PTR was associated with high postoperative morbidity and mortality rates in the presence of metastases[12,45,82] (Table 5). One study reported that 15 of 128 patients (11.7%) patients died within 30 d postoperatively[45]. However, in this study many patients were symptomatic and underwent emergency surgery. The same series found a 27.8% mortality rate in patients who had emergency surgery *vs* only 7.3% mortality rate with elective procedure ($P = 0.002$)[45]. The high postoperative mortality rate of 5% reported by Scoggins *et al*[82] included patients who were symptomatic at the time of resection and the patient who died after surgery were noted to have severe carcinomatosis.

These mortality rates were higher that noted in the recently published meta-analysis where collectively, perioperative mortality was 1.7% (95%CI: 0.7-3.9)[8]. This lower mortality rate can be accounted for the preeminent number of patients that were asymptomatic and managed electively. In this meta-analysis, postoperative morbidity occurred in 23% (95%CI: 18.5-21.8) of patients. The most frequent complication was wound infection and could be mostly managed conservatively; however, in some instances, major complication arose whereby patients required additional surgery as management. Anastomotic leakage, occurring in 1.7% of patients, is more commonly a significant complication of rectal cancer resection. It often leads to sepsis, significantly prolongs hospital stay and delay or even precludes chemotherapy administration[8].

In a recent large monocentric series, this same group analyzed the postoperative outcomes in 379 CRC patients with unresectable synchronous metastases undergoing PTR[31]. In the postoperative period, mortality and morbidity rates were 9.2% and 48.3%, respectively. Postoperative surgical and medical complication rates were 35.6% and 25.3%, respectively. Among these patients, 33 required one or more reinterventions in the same admission to manage these complications. The most common surgical complications included wound infections and the most common medical complications comprised respiratory events followed by cardiac events. However, 45% of patients were aged of more than 70 years in this series, 60% had a locally advanced primary tumor and nearly 30% had rectal cancer[31].

These results need to be interpreted with caution as these studies suffered from several limitations. Firstly, morbidity rates were not always separated between minor and severe complications. Secondly, inclusion periods were very long and progresses in surgery and postoperative care have not been taken into account. In a recent series of 313 patients treated for unresectable synchronous stage IV CRC over different time periods, Platell *et al*[83] reported that the 30-d postoperative mortality (12.6% *vs* 2.7%, $P = 0.036$) and the duration of hospital stay (13 d *vs* 9 d, $P = 0.026$) have decreased significantly from 1996-2002 to 2003-2009 periods, despite increased numbers (28% *vs* 46.4%, $P = 0.001$) of patients with severe comorbidity (*i.e.*, ASA score 3 or 4). Another limitation resides in the heterogeneity of populations, as studied patients included those with symptomatic or locally advanced primary tumor, patients with rectal primary, patients with advanced age and severe comorbities, those with extensive and extra-hepatic metastatic spread or patients with poor general condition[8,31]. Fourthly, in all but two studies[31,46], there was no mention of the use of laparoscopy in patients electively undergoing PTR, which has been convinced to decrease postoperative morbidity compared to laparotomy. Indeed, in several phase Ⅲ trials, overall surgical morbidity following elective colectomy for cancer was 0.7%-3% and 20%-28%, in patients operated with laparoscopy and laparotomy, respectively[84]. Finally, one should note that in all series reporting the postoperative outcome after PTR in stage Ⅳ CRC patients, there was no mention of the use of perioperative immunonutrition which has also been demonstrated to improve postoperative outcomes in patients operated for various types of digestive cancers[85].

Few studies have performed a multivariate logistic regression analysis to determine independent factors associated with postoperative mortality and morbidity in patients with stage IV CRC. In the series reported by Stelzner *et al*[45] postoperative mortality (11.7%) was not associated with PTR but was significantly related to ASA score IV (ASA score III, 7% *vs* ASA score IV, 26.4%, $P = 0.002$), higher age (≤ 75 years, 7.6% *vs* > 75 years, 20%, $P = 0.015$) and emergency operations (27.8%, *vs* elec-

tive, 7.3%, $P = 0.002$). In the largest series of 379 resected patients with an unresectable stage Ⅳ CRC, Stillwell *et al*[31] found that at multivariate analysis, 30-d postoperative mortality was independently associated with medical complications ($P < 0.001$), emergency interventions ($P = 0.001$) and age (≥ 70 years, $P = 0.007$). Conversely, patients with liver-only metastases were less likely to die in the postoperative period than those with advanced local disease and/or extra-hepatic disease ($P = 0.004$). In this large series, emergency interventions were also linked to morbidity, a fact that is well established in literature[45,68-70]. In another series, independent determinants of an increased postoperative morbidity (total rate of 46%) were primary rectal cancer, hepatic tumor involvement > 50%, and comorbidity > 1 organ[46].

To summarize, after palliative PTR in metastatic patients, most studies suggested that baseline characteristics (age, WHO-PS, comorbidity, ASA score), advanced local and metastatic disease and rectal primary tumor to be related to postoperative morbidity and mortality. Taken together, these findings suggest that one issue for a phase Ⅲ study would be to assume that the acceptable risks of postoperative mortality and severe morbidity rates would be less than 10% and 30%, respectively. These rates could be even lower with the use of laparoscopic approach, which is known to improve short-term outcomes, including postoperative morbidity, compared to open surgery[23-25,86]. Besides, perioperative nutrition should be systematically recommended. Finally, these anticipated morbidity and mortality rates are those expected in a population of selected patients, constituted after the exclusion of patients which would not be likely to benefit from PTR (patients in poor general condition, with severe comorbidities, rectal cancer, extra-hepatic metastatic disease, complicated primary tumor).

SPECIFIC ISSUES OF RECTAL CANCER

By its particular location in the pelvis, rectal cancer differs from colon cancer on several points: first, unresected rectal tumors can lead to disabling symptoms (pelvic pain, rectal syndrome) and local related complications such as urinary obstruction, perforation with pelvic abscess or recto vaginal fistula that can be disastrous and difficult to manage; secondly, for locally advanced mid and/or low rectal tumors (*i.e.*, staged cT3, T4 and/or cN-positive disease) neoadjuvant treatment (short-course radiotherapy (RT) or long-course chemoradiotherapy) has been demonstrated to decrease the risk of local recurrence with no effect on survival; finally rectal resection with total mesorectal excision is a demanding surgery with high postoperative complications rates (which may delay or even preclude chemotherapy administration), risk of long-term functional disorders (digestive, sexual, urinary) that can negatively impact on quality of life and lead to permanent stoma in up to 20% of operated patients[87].

In patients with rectal cancer and synchronous unresectable metastases, up-front chemotherapy administration before considering the need to resect the primary tumor may represent an attractive therapeutic option for the following reasons: surgery (with or without neoadjuvant treatment) is avoided in patients with rapidly progressive metastatic disease which should be regarded as a biological marker for poor prognosis and an indication for administering second-line treatment. In a retrospective study of 22 patients with rectal cancer and unresectable synchronous metastases, Stelzner *et al*[88] reported that, in patients without progression under first-line chemotherapy, median OS was significantly increased in patients who underwent PTR compared to those with the primary tumor left in place (27.2 mo *vs* 12.4 mo, $P = 0.017$). In addition, systemic chemotherapy has also an effect on primary tumor in rectal carcinoma. In a phase 2 trial evaluating neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in 105 patients with locally advanced rectal cancer, Chua *et al*[89] emphasized that morphological reevaluation after neoadjuvant chemotherapy showed an objective response in 78 patients (74%). Based on these results, patients could receive short-course RT or even no RT at all before rectal surgery in case of partial or complete radiological response after neoadjuvant chemotherapy. In conclusion, for patients with rectal cancer and unresectable SLM, it seems relevant that chemotherapy should be the first treatment and surgery should only be proposed when there is no progression during preoperative chemotherapy. Patients with a poor prognosis due to progressive metastatic disease are thereby spared the risks of major rectal surgery with a long hospital stay and unnecessary surgical complications.

DISCUSSION: WHAT DESIGN FOR A STUDY ATTEMPTING TO ANSWER THIS ISSUE?

Whether PTR should be performed prior chemotherapy administration in unresectable stage Ⅳ CRC patients remains unknown. When the primary tumor is not resected and uncomplicated (asymptomatic) and the patient has started with palliative chemotherapy, the rate of unplanned or emergency surgery is relatively low and therefore does not warrant surgery of the primary in future patients. This relative low rate of primary tumor-related complications under chemotherapy may be partly explained by the effectiveness of chemotherapy regimens and targeted agents. With regard to survival, most retrospective studies favor PTR, but results are likely to be influenced by selection biases. These studies suggested that liver burden > 50%-75%, extra-hepatic metastatic disease (peritoneal carcinomatosis, lung metastases), advanced age and poor WHO-PS were poor prognostic factors in CRC patients with unresectable SLM even for those who undergo PTR. These factors, in addition to rectal primary location, have also been reported to be associated with high postoperative mortality and morbidity following PTR. In summary, data from the literature highlight that patient selection taking into account all the above men-

tioned factors is a critical issue for a future randomized trial aiming to determine whether OS is improved by PTR in patients with CRC and unresectable liver metastastic.

Definition of metastases unresectability is also a critical issue. Among patients with CRC liver metastases, no consensual precise definition of resectability or unresectability has been reached to date[3]. The resectability of liver metastases may differ from one hospital to another, depending on the available equipment and the level of surgical expertise. The definition also depends, understandably, on patient-specific data, such as general health, comorbidities, nutritional status, and more specifically, the presence of a possible underlying liver disease. For these reasons and to provide a rigorous framework, a relevant definition of liver metastases unresectability would be the inability to achieve a macroscopically complete resection (with clear margins) of all metastases, in one- or two-stage, without compromising postoperative liver function because of the insufficiency of either the remaining liver volume or biliary and venous vascularization and drainage. Unresectability of liver metastases would have to be assessed on a helical or multi-slice abdominal CT-scan with contrast enhancement, or liver MRI if CT is impossible (kidney failure, allergy to iodine) or insufficient to characterize lesions[81]. Radiological criteria for liver metastases unresectability would gather involvement of all hepatic veins, or both portal branches, or one portal branch and the controlateral hepatic vein(s), and a predictable post-hepatectomy liver volume < 25%-30%.

Then, all eligible patients would be randomized to undergo either PTR followed by chemotherapy ± targeted agent or chemotherapy ± targeted agent without PTR. Randomization would be stratified according to the study center and the metastatic liver involvement (≤ 50% *vs* > 50%) as determined by the pretreatment CT-scan or liver MRI staging.

The primary endpoint would be the difference in OS between the two treatment arms. Secondary endpoints would be quality of life, rate of primary tumor-related complications in the arm with chemotherapy alone and postoperative morbidity in the PTR arm. Besides, the tolerability of chemotherapy, objective tumor response, PFS, time to metastatic progression and the rate of secondary curative resection (R0) of both the primary and metastases should be assessed in both treatment arms.

No randomized study has been performed yet. The entire international community wishes to answer this question. One should emphasized that since 2010 until today, 14 papers on the present subject have been published including 9 individual series, 5 reviews or meta-analyses, 1 editorial and 1 guidelines from the French authorities. In all these publications, the need to perform a randomized trial evaluating the impact of PTR on survival in patients with CRC and unresectable metastases is underlined.

CONCLUSION

The present review assessed whether OS and quality of life are improved in patients with asymptomatic unresectable metastatic CRC treated with surgery followed by chemotherapy *vs* chemotherapy alone with the primary in place. Reported data from the literature support the view that PTR should be discussed and validated by a phase III trial in selected patients: asymptomatic primary tumor, age ≤ 70 years, WHO-PS < 2, no extra-hepatic metastatic disease, liver burden of less than 50%. In these patients, PTR, when performed laparoscopically and after preoperative immuno-nutrition, may lead to an increased OS. In all other cases, reported postoperative mortality and morbidity rates related to PTR are high and up-front chemotherapy with the primary tumor left in place may represent the more reasonable option.

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