

Treatment strategy for colorectal cancer with resectable synchronous liver metastases: Is any evidence-based strategy possible?

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Abstract

Fifteen percent to twenty-five percent of patients affected by colorectal cancer presents with liver metastases at diagnosis. In resectable cases, surgery is the only potentially curative treatment and achieves survival rates up to 50% at 5 years. Management is complex, as colorectal resection, liver resection, chemotherapy, and, in locally advanced mid/low rectal tumors, radiotherapy have to be integrated. Modern medical practice usually relies on evidence-based protocols. Levels of evidence for synchronous metastases are poor: published studies include few recent prospective series and several retrospective analyses collecting a limited number of patients across long periods of time. Data are difficult to be generalized and are mainly representative of single centre's experience, biased by local recruitment, indications and surgical technique. In this context, surgeons have to renounce to "evidence-based medicine" and to adopt a sort of "experience-based medicine". Anyway, some suggestions are possible. Simultaneous colorectal and liver resection can be safely performed whenever minor hepatectomies are planned, while a case-by-case evaluation is mandatory in case of more complex procedures. Neoadjuvant chemotherapy is preferentially scheduled for patients with advanced metastatic tumors to assess disease biology and to control lesions. It can be safely performed with primary

tumor *in situ*, even planning simultaneous resection at its end. Locally advanced mid/low rectal tumor represents a further indication to neoadjuvant therapies, even if treatment's schedule is not yet standardized. In summary, several issues have to be solved, but every single HPB centre should define its proper strategy to optimize patient's selection, disease control and safety and completeness of surgery.

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Key words: Synchronous liver metastases; Colorectal liver metastases; Liver surgery; Simultaneous colorectal and liver resection; Preoperative chemotherapy; Up-front chemotherapy; Neoadjuvant chemo-radiotherapy; Locally advanced rectal cancer; Survival

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INTRODUCTION

Fifteen to 25% of patients affected by colorectal cancer presents with liver metastases at diagnosis^[1,2]. In resectable cases, surgery is the only potentially curative treatment^[3-5] and achieves survival rates up to 50% at 5 years^[6,7]. Management is complex, as colorectal resection, liver resection, chemotherapy, and, in locally advanced mid/low rectal tumors, radiotherapy have to be integrated.

Modern medical practice usually relies on evidence-based protocols. Levels of evidence for synchronous metastases are poor: published studies include few recent prospective series and several retrospective analyses collecting a limited number of patients across long periods of time. Data are difficult to be generalized and are mainly representative of single centre's experience, biased by local recruitment, indications and surgical technique. In this context, surgeons have to renounce to "evidence-based medicine" and to adopt a sort of "experience-based medicine"^[8].

SIMULTANEOUS COLORECTAL AND LIVER RESECTION: IS IT BENEFICIAL OR DETRIMENTAL?

The timing of colorectal and liver surgery (simultaneous *vs* staged) has been debated since the 1980s. Theoretically, simultaneous resections have an increased risk of both anastomotic leak (splanchnic congestion after liver surgery) and liver failure (septic complications due to the combination of "clean" and "contaminated" procedures)^[9-11]. These fears had not been confirmed in recent studies that reported similar outcomes after simultaneous and delayed resections^[7,12-19]. Anyway, the debate is still open: favorable data concerned "easy" resections. What about simultaneous major hepatectomies?

The largest available series are summarized in Table 1. In 2007, Capussotti *et al*^[20] compared 31 simultaneous major liver resections with 48 staged ones. Mortality rates were similar in the two groups; considering the two hospitalizations of delayed resections, morbidity and hospital stay resulted even lower in the simultaneous group (33% *vs* 56% and 14 d *vs* 20 d, respectively). These data have been recently confirmed by a few other series^[15,21]. On the contrary, a US multicentre database reported increased mortality and morbidity rates after simultaneous major hepatectomy (8% *vs* 1% and 44% *vs* 27%, respectively)^[18]. How to conciliate these discrepancies? It is an unsolved question. Simultaneous resections can be neither recommended nor contraindicated. Obviously, patient's selection is mandatory to achieve good outcomes. Particular attention should be paid to the elderly patients, who experienced the worst outcomes^[22,23]. Thus, in the absence of evidence and avoiding dogmatic positions, every single centre may adopt its proper preferred policy.

PREOPERATIVE CHEMOTHERAPY: SYSTEMATIC VS SELECTIVE INDICATIONS

Even if surgery is the optimal treatment of patients with colorectal metastases, some resectable patients do not benefit from immediate resection because of rapidly progressive disease or of microscopic neoplastic foci that lead to early recurrence^[24,25]. How to select good

candidates? A time test, i.e., an interval of time before resection, has been proposed. At present, neoadjuvant chemotherapy is the standard time test, allowing tumor biology evaluation, disease control and microscopic foci sterilization^[26].

Despite strong theoretical advantages, practical evidences are weak. In 2008 a RCT compared outcomes of patients undergoing surgery with or without perioperative chemotherapy: treated patients had higher disease-free survival rates, but effects of pre- and postoperative chemotherapy resulted indistinguishable^[26]. Two retrospective series, specifically focused on synchronous metastases, failed to demonstrate any survival advantage in patients receiving systematic neoadjuvant treatments^[27,28].

Selective indications might be adopted. The presence of more than three lymph node metastases has been proposed, but this criterion is difficult to be preoperatively ascertained^[29]. In 2007 a study by the author's centre demonstrated that preoperative treatment was useful for selecting patients with T4 primary tumors or with more than three metastases^[30]. Additional indications can be proposed on a logical basis: ill-located lesions (disease shrinkage enables easier R0 resection) and presence of extra-hepatic disease. Further studies are needed to codify these indications.

IS SIMULTANEOUS COLORECTAL AND LIVER SURGERY SYNONYMOUS FOR IMMEDIATE RESECTION?

If neoadjuvant chemotherapy is scheduled, the commonest strategy is colorectal surgery followed by chemotherapy, and then liver surgery^[31,32]. In the past, the anticipated risk of intestinal occlusion while on therapy precluded any possibility to plan simultaneous resection at the end of treatment. Some authors even criticized simultaneous surgery because of the impossibility to perform any patient's selection^[24,25,33].

At present, simultaneous resection is no more synonymous for immediate resection at diagnosis. Recent series demonstrated that up-front chemotherapy with primary tumor *in situ* could be safely administered in unresectable patients^[34-40]. The occlusion risk is low, mainly thanks to the effectiveness of modern chemotherapies on primary tumor (Table 2). Furthermore, endoscopic metallic stents may treat symptomatic patients before chemotherapy or even while on treatment^[41].

Similar outcomes can be expected in resectable patients. However, only few published simultaneous resections have been preceded by chemotherapy. In the author's centre this strategy has been regularly applied since many years. A retrospective analysis of 40 consecutive patients scheduled for up-front chemotherapy followed by simultaneous colorectal and hepatic resection between 2005 and 2009 demonstrated that a disease control was achieved in 97.5% of patients, an obstructive syndrome occurred in only 7.5%, a simultaneous resection was

Table 1 Outcome of simultaneous *vs* staged major liver resections

Author	Year	Patients		Mortality			Morbidity		
		SimRes	Del	SimRes (%)	Del (%)	P value	SimRes (%)	Del (%)	P value
Martin <i>et al</i> ^[15]	2003	45	76	4	4	NS	60	70	0.03
Thelen <i>et al</i> ^[22]	2007	15	142	26.7	1.4	0.0007	NR	NR	
Reddy <i>et al</i> ^[18]	2007	36	291	8.3	1.4	0.03	44.4	26.8	0.04
Capussotti <i>et al</i> ^[20]	2007	31	48	3.2	0	NS	32.6	56.3	0.04
de Santibañes <i>et al</i> ^[23]	2010	42	-	4.7	-	-	37.2	-	-
Luo <i>et al</i> ^[21]	2010	44	133	NR	NR		56.8	57.1	NS

¹In delayed liver resections, morbidity of both hospitalizations (colorectal surgery and liver surgery) is considered; ²Simultaneous colorectal and major liver resection *vs* other isolated liver resections. SimRes: Simultaneous colorectal and major liver resection; Del: Delayed major liver resection; NR: Data not reported; NS: Not significant.

Table 2 Outcome of “Up-front chemotherapy” strategy: risk of emergency surgery while on treatment *n* (%)

Author	Year	Patients	Resectable at diagnosis	Oxaliplatin- or Irinotecan-based chemotherapy (%)	Emergency surgery
Benoist <i>et al</i> ^[37]	2005	27	No	67	4 (14.8)
Muratore <i>et al</i> ^[38]	2007	35	No	100	1 (2.8)
Poultides <i>et al</i> ^[39]	2009	233	No	100	16 (7)
Karoui <i>et al</i> ^[40]	2011	123	No	90	15 (12.1)
Viganò/Capussotti ¹	2012	40	Yes	100	3 (7.5)

¹Unpublished data.

feasible in 95%, and the 3-year survival rate was 75% (unpublished data). These promising results need to be validated by larger prospective studies.

METASTATIC LOCALLY ADVANCED MID/LOW RECTAL CANCER: WHAT ABOUT RADIOTHERAPY?

Neoadjuvant chemo-radiotherapy is the gold standard for patients with non-metastatic locally advanced (T3-4 and/or N+) mid/low rectal cancer to reduce local relapse^[42,43]. The inclusion of radiotherapy in the treatment of metastatic patients presents some problems, as high-dose systemic chemotherapy regimens are needed to control hepatic disease, but chemotherapy doses must be reduced in association with radiations in order to limit toxicity^[44]. Currently, there is no consensus about the optimal treatment.

In 2006, Mentha *et al*^[45] proposed a “reverse” strategy, i.e., a two-stage surgery with liver resection as the first procedure. It easily enables the inclusion of radiations before rectal surgery (the second surgical step). Encouraging results were reported (4-year survival rate of 56%). In 2001 a cooperative study between the author’s centre and the Cherqui one (Henri Mondor Hospital, Créteil, France) collected 36 patients^[46]. The adopted strategy was up-front neoadjuvant chemotherapy and/or chemo-radiotherapy, according to liver disease extension, followed by simultaneous rectal and liver resection. Five-year survival rate was 59% and no pelvic recurrence occurred among patients who correctly completed the treatment

strategy. Further, systemic chemotherapy achieved primary tumor downsizing in most cases, questioning the real need for radiations.

Stronger evidences are needed to consider any possible strategy as the optimal one.

CONCLUSION

No evidence-based conclusions can be drawn, but some suggestions are possible. Simultaneous colorectal and liver resection can be safely performed whenever minor hepatectomies are planned, while a case-by-case evaluation is mandatory in case of more complex procedures. Neoadjuvant chemotherapy is preferentially scheduled for patients with advanced metastatic tumors to assess disease biology and to control lesions. It can be safely performed with primary tumor *in situ*, even planning simultaneous resection at its end. Locally advanced mid/low rectal tumor represents a further indication to neoadjuvant therapies, even if treatment’s schedule is not yet standardized.

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