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REVIEW ARTICLE

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Optimal patient selection for successful two-stage hepatectomy of bilateral colorectal liver metastases

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Abstract

Two-stage hepatectomy (TSH) is one of the specific surgical techniques that can expand the pool of resectable patients with initially unresectable colorectal liver metastases (CRLM). The indication of TSH for CRLM is only bilateral, multinodular disease, which cannot be resected by a single hepatectomy. TSH is nowadays considered an effective treatment for selected patients, with acceptable morbidity/mortality rates and promising long-term outcomes. However, not all eligible patients can benefit from the TSH strategy. One of the most important issues is dropout from the strategy (failure to complete both of the two sequential procedures), because the survival of such patients is drastically worse compared with patients who can complete both stages. Another important issue is the early recurrence rate and subsequent poor survival even after completion of TSH. Thus, the selection of appropriate patients who can really benefit from the TSH strategy is crucial. This review discusses the optimal patient selection for TSH, which should be helpful for the development of treatment strategies for patients with extensive CRLM.

KEYWORDS

colorectal liver metastases, patient selection, two-stage hepatectomy

1 | INTRODUCTION

The liver is the most common organ of metastases from colorectal cancer. Liver metastases are present in 15%–25% of patients with colorectal cancer at the time of diagnosis, and another 25%–50% will develop liver metastases during the course of their disease.[1–3] Although hepatic resection is still the only treatment of choice that can ensure prolonged survival, only 20%–30% of patients with colorectal liver metastases (CRLM) are initially determined to be eligible for surgery.[4,5] Expanding the potentially resectable pool of patients is therefore considered important.

Nowadays, the number of patients who are candidates for hepatic resection has dramatically increased because of the advent of more effective chemotherapy with biologic agents and the development of specific surgical techniques, based on multidisciplinary approaches.[6] Two-stage hepatectomy (TSH) is one such specific surgical technique that can expand the pool of resectable patients with CRLM. The concept of TSH was first introduced by the Paul Brousse team in 2000,[7] and has evolved in combination with portal vein embolization (PVE) / portal vein ligation (PVL) and effective chemotherapy. TSH typically consists of two sequential stages of operation: 1) in the first stage, the less invaded liver lobe (future liver remnant

[FLR], usually the left lobe) is cleaned of its metastases in combination with contralateral PVE/PVL to induce FLR hypertrophy; and 2) in the second stage, the tumor-bearing liver lobe (deportalized liver lobe) is anatomically removed.[6] The interval duration between the first- and second-stage is reported to be 32–210 d.[8] The sole indication of TSH is bilateral multinodular disease that is not amenable to complete removal by a single hepatectomy, even in combination with chemotherapy, PVE, and local ablation therapy. TSH is nowadays accepted as an effective treatment for selected patients with initially unresectable multiple bilobar CRLM, achieving a 5-year survival rate of 32%–64%.[9–17] However, not all eligible patients can benefit from this strategy, because of either dropout from the second-stage hepatectomy or early recurrence after surgery, and subsequently poor survival. In this review, we discuss optimal patient selection for TSH, which is crucial for the development of this treatment strategy for patients with extensive CRLM.

2 | INDICATION OF TSH FOR CRLM

TSH is indicated for bilateral, multinodular disease that is not amenable to complete removal by single hepatectomy, even with PVE and local ablation therapy. Basically, TSH is performed in combination with preoperative chemotherapy. When all tumors can be treated by a single hepatectomy using parenchyma-preserving hepatectomy or by resection combined with local ablation therapy, TSH is not indicated.

The presence of extrahepatic metastases is usually not considered a contraindication for hepatectomy if these metastases are limited and resectable (or sometimes controllable under chemotherapy). In the relevant literature, 3%–29% of CRLM patients who were submitted to surgery were planned for TSH.[9–11,14,15,18–23]

3 | PATIENT SELECTION: FROM THE VIEWPOINT OF DROPOUT

The main drawback of TSH is the failure to complete both sequential procedures. This dropout rate was reported to be 0%–36% (median, 23%), and the main reason for failure was disease progression between the two stages (56%–100%), which correlated with the severity of the tumoral disease.[24] We previously reported that among 125 patients with bilateral, multinodular CRLM who were planned for TSH, 44 patients could not proceed to the second stage (dropout rate 35.2%). The reasons for dropout were 1) tumor progression (39 patients, 88.6%), 2) insufficient FLR volume (three patients, 6.8%), poor general condition (one patient, 2.3%), and mortality after the first stage (one patient, 2.3%; 1/125 = 0.8%).[22] The overall survival (OS) after first-stage hepatectomy in patients who dropped out was significantly worse than in those who completed (5-year OS rate: 0% vs 44.2%, $P < .0001$). Therefore, to reduce the dropout rate is crucial in this strategy, and to do so, how to prevent disease progression between the two stages is important. For this reason, our team is routinely reintroducing interval chemotherapy; however, this policy is not shared by all teams, with 13%–100% and a mean of only 37% of patients receiving such interval treatment.[25] So far, several predictive factors for dropout from the strategy of TSH have been identified, including patient-related, disease-related, surgery-related, and chemotherapy-related factors (Table 1).[10,12,15,16,22,23,26–28] These factors may help surgeons to predict the dropout risk for patients who are submitted to TSH. In our previous study, four factors were identified as independent predictors of dropout from TSH: disease progression on first-line chemotherapy, number of chemotherapy cycles >12, largest tumor size >40 mm, and carcinoembryonic antigen (CEA) at hepatectomy >30 ng/mL.[22] Accordingly, a predictive model for dropout using these four factors was determined, based on a logistic model (Table 2). For patients without any factors, the probability of dropout was 10.5%. The addition of subsequent risk factors increased the probability of dropout to 24.3%–43.5% for one factor, 48.1%–72.7% for two factors, 76.2%–88.5% for three factors, and 95.5% for four factors. This predictive model can contribute to a better patient selection for optimal candidates for TSH.

4 | PATIENT SELECTION: FROM THE VIEWPOINT OF PROGNOSIS

Previous studies reported several prognostic factors in patients who were submitted to TSH (Table 3).[11–13,26,27,29,30] As mentioned above, completion of both sequential procedures of TSH is crucial for long-term outcome; thus, dropout from TSH completion is of paramount importance for prognosis.[11,22,26–28] On the other hand, in the TSH-completed cohort, tumor number >6,[27,29] concomitant extrahepatic disease,[29] no postoperative chemotherapy,[30] chemotherapy cycle ≥6,[12] major complication at second stage,[6] no repeat surgery for recurrence,[13,30] first recurrence at multiple sites,[30] and *RAS* mutation[16] were reported as independent prognostic factors for poor survival after TSH. Because these reports were based on retrospective analyses, it is difficult to state the proper prognostic roles of these factors. However, these factors may be somewhat helpful for optimal selection of patients who are submitted to TSH.

5 | PATIENT SELECTION: FUTURE PERSPECTIVES FROM THE VIEWPOINT OF MOLECULAR PROFILE

CRLM is a heterogeneous disease with several possible pathways responsible for carcinogenesis and multiple genetic mutations. Molecular biomarkers nowadays play crucial roles in risk stratification and decision-making for treatment. *KRAS* and *BRAF* mutation are probably the most well-investigated biologic markers. A recent systematic review demonstrated that *KRAS* and *BRAF* are negatively associated with disease relapse and survival after resection of CRLM.[31] *RAS* mutation has also been found to confer worse survival in patients who underwent surgical resection for CRLM.[31]

TABLE 1 Predictive factors for dropout from the strategy of TSH

Study	Year	Country	No. of patients	Dropout rate (%)	Predictive factors for dropout	
					Univariate	Multivariate
Tsai et al	2010	USA	45	22	Higher tumor number No preoperative chemo	ND
Narita et al	2011	France	76	20	Age ≥70 ≥3 tumors in the FLR CEA >200 (ng/mL) before PVE	Age ≥70 ≥3 tumors in the FLR
Turrini et al	2012	France	42	19	Combined resection of primary tumor Interval chemotherapy	Combined resection of primary tumor
Giuliante et al	2014	Italy	126 (multicenter)	22	Disease progression during chemo	Disease progression during chemo
Faitot et al	2015	France	50	24	Male gender Vascular invasion on primary >5 tumors Segment 1 metastases Need for chemo change Need for >3 curative treatments Microscopic biliary invasion	Nothing
Imai et al	2015	France	125	35	CEA >30 (ng/mL) Tumor size >40 (mm) No. of chemotherapy cycles >12 No. of chemotherapy lines >1 Disease progression during 1st-line chemo	CEA >30 (ng/mL) Tumor size >40 (mm) No. of chemotherapy cycles >12 Disease progression during 1st-line chemo
Passot et al	2016	USA	109	18	Tumor size >50 (mm) No. of chemotherapy cycles >6	No. of chemotherapy cycles >6
Regimbeau et al	2017	worldwide	869 (multicenter)	28	No repeat hepatectomy Extrahepatic metastasis Non-R0 resection at first-stage No preoperative chemo	ND
Quénet et al	2018	France	56	38	TRG 4/5 mTRG 4/5 Blazer classification 2 Tumor number >6	Blazer classification 2 Tumor number >6

Abbreviations: CEA, carcinoembryonic antigen; FLR, future liver remnant; mTRG, modified tumor regression grade; ND, not done; PVE, portal vein embolization; TRG, tumor regression grade; TSH, two-stage hepatectomy.

In addition, prognostic roles for alterations in genes other than *RAS* and *BRAF* have also been reported, such as *CDX2*,[32] *TP53*,[33] and *SMAD4*.[34] However, few studies have investigated the prognostic role of biologic markers in patients who underwent TSH for CRLM. Passot et al reported that *RAS* mutation was independently associated with poorer survival and they postulated that the long-term survival benefit of TSH is limited in patients with the *RAS* mutation.[27] Lillemoe et al investigated 83 patients who developed recurrence after TSH, and found that *RAS* mutation was an independent predictor of worse survival.[30] These results suggest that knowledge of the *RAS* mutation status can be helpful for optimal selection of patients who are submitted to TSH. Further studies evaluating the prognostic impact of several biologic markers in patients who are candidates for TSH are warranted for optimal patient selection.

6 | CONCLUSION

For patients with extensive bilateral multinodular CRLM, TSH is a potential treatment of choice for prolonged survival. However, not all eligible patients can benefit from this strategy. Herein we summarize the optimal patient selection from the view point of three aspects, including "dropout," "prognosis," and "molecular profile." Optimal patient selection criteria for patients who are submitted to a TSH strategy should be developed based on the factors associated with dropout and prognosis. Personalized precision medicine based on a multidisciplinary approach, including molecular markers, will have an important place in the TSH strategy in the future.

DISCLOSURE

Conflicts of Interest: The authors declare no conflicts of interest.

TABLE 2 Predictive model for dropout from the strategy of two-stage hepatectomy based on four factors identified by multivariate logistic regression analysis (Ref.22 with permission)

Factors	CEA at hepatectomy >30 (ng/mL)	Tumor size at hepatectomy >40 (mm)	Chemotherapy cycles before hepatectomy >12	Tumor progression during 1st-line chemotherapy	Probability (%)
0	−	−	−	−	10.5
1	+	−	−	−	25.3
	−	+	−	−	24.3
	−	−	+	−	28.9
	−	−	−	+	43.5
2	+	+	−	−	48.1
	+	−	+	−	54.0
	+	−	−	+	69.0
	−	+	+	−	52.6
	−	+	−	+	67.8
	−	−	+	+	72.7
3	+	+	+	−	76.2
	−	+	+	+	87.9
	+	−	+	+	88.5
	−	+	+	+	87.9
4	+	+	+	+	95.5

Abbreviation: CEA, carcinoembryonic antigen.

TABLE 3 Independent prognostic factors for survival after TSH

Study	Year	Country	No. of pts.	5-y OS	Independent prognostic factors (multivariate)	Patient cohort
Wicherts et al	2008	France	41	42	Tumor number ≥6 Concomitant extrahepatic disease No postoperative chemotherapy	TSH completed cohort
Brouquet et al	2011	USA	62	51	Major complication after first- or second-stage TSH failure	whole cohort
Giuliante et al	2014	Italy	102	32	Chemotherapy cycle ≥6	TSH completed cohort
Faitot et al	2015	France	50	27 (3-y)	TSH failure	whole cohort
Passot et al	2016	USA	109	49 (completed)	Rectal primary Tumor number ≥6 Interval chemo after first-stage *RAS* mutation	whole cohort
Imai et al	2019	France	93	41.3	Major complication at second-stage No repeat surgery for recurrence	TSH completed cohort
Lillemoe et al	2019	USA	83	47	No repeat surgery for recurrence First recurrence at multiple sites *RAS* mutation	TSH completed cohort (patients with recurrence)

Abbreviations: OS, overall survival; TSH, two-stage hepatectomy.

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