



## Drop-out between the two liver resections of two-stage hepatectomy. Patient selection or loss of chance?

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### Abstract

**Background:** Two-stage hepatectomy (TSH) is the present standard for multiple bilobar colorectal liver metastases (CLM), but 25–35% of patients fail to complete the scheduled procedure (drop-out). To elucidate if drop-out of TSH is a patient selection (as usually considered) or a loss of chance.

**Methods:** All the consecutive patients scheduled for a TSH at the Paul Brousse Hospital between 2000 and 2012 were considered. TSH patients were matched 1:1 with patients receiving a one-stage ultrasound-guided hepatectomy (OSH) at the Humanitas Research Hospital in the same period. Matching criteria were: primary tumor N status; timing of CLM diagnosis; CLM number and distribution into the liver. **Results:** Sixty-three pairs of patients were analyzed. Demographic and tumor characteristics were similar (median 7 CLM), except for more chemotherapy lines and adjuvant chemotherapy in TSH. Drop-out rate of TSH was 38.1% (0% of OSH). The two groups had similar R0 resection rate (19.0% OSH vs. 15.9% TSH). OSH and completed TSH had similar five-year survival (from CLM diagnosis 49.8% vs. 49.7%, from liver resection 36.1% vs. 44.3%), superior to drop-out (10% three-year survival,  $p < 0.001$ ). OSH and completed TSH had similar recurrence-free survival (at three years 21.7% vs. 20.5%) and recurrence sites. The completion of resection (drop-out vs. OSH/completed TSH) was the only independent prognostic factor ( $p = 0.003$ ).

**Conclusions:** Drop-out of TSH could be a loss of chance rather than a criteria for patient selection. “Unselected” OSH patients had the same outcomes of selected patients who completed TSH. A complete resection is the main determinant of prognosis.

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**Keywords:** Colorectal liver metastases; Two-stage hepatectomy; One-stage hepatectomy; Overall survival and recurrence-free survival; Drop-out; Surgical margin

### Introduction

Liver resection (LR) for colorectal liver metastases (CLM) is indicated whenever a complete resection with adequate future liver remnant (FLR) is possible.<sup>1,2</sup> In patients with multiple unresectable bilobar CLM, Adam et al. proposed the “two-stage hepatectomy” (TSH)

approach.<sup>3</sup> It schedules two subsequent hepatectomies with hypertrophy of FLR in between to combine safety (prevention of liver dysfunction) and efficacy (complete disease clearance). This approach achieved excellent results, i.e., low mortality and morbidity rates and good long-term outcomes, similar to standard hepatectomies.<sup>4–10</sup>

The main drawback of TSH is the risk of drop-out after the first LR: 25–35% of patients do not complete the treatment strategy, mainly because of disease progression between the two stages.<sup>5,11</sup> In the majority of patients, the drop-out has been considered a sort of selection of patients with rapidly progressive disease. They would probably have not benefited from surgery. The poor prognosis of patients who did not

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complete TSH and the excellent outcomes of patients who completed TSH seem to confirm this hypothesis. Nevertheless, it could not be the case. The liver hypertrophy after the stage one induced by portal vein occlusion (PVO) could facilitate neoplastic proliferation and progression.<sup>12,13</sup> This risk is even more relevant if combined with postoperative immunosuppression.<sup>14</sup> A clinical model suitable for validating or not the hypothesis that staged approach allows patient selection exists, the ultrasound-guided and parenchyma-sparing one-stage hepatectomy (OSH) of multiple CLM. A single-stage hepatectomy is generally performed for subglissonian CLM requiring multiple limited resections.<sup>15,16</sup> OSH has been recently proposed to face deep-located CLM with major vascular contacts.<sup>17</sup>

The present study is a retrospective case-control analysis comparing the long-term outcomes of patients scheduled for TSH with those of patients undergoing the aforementioned OSH. The patients were matched to have similar tumor features. The aims of the study were: 1) to elucidate if drop-out patients of TSH would have benefited from a complete resection (loss of chance); 2) to clarify if patients who completed TSH have better oncological results in comparison with those of “unselected” OSH patients (patient selection).

## Methods

All the 122 consecutive patients scheduled for a TSH for multiple bilobar CLM at the Paul Brousse Hospital, Villejuif, France (PBH) between January 2000 and December 2012 were considered. Thirty-three patients with simultaneous extra-hepatic distant metastases were excluded, as well as 6 receiving intraoperative radiofrequency ablation. Finally, all the 83 consecutive patients with liver-only disease receiving a pure surgical treatment into a TSH strategy were retained.

In the same period, 93 patients affected by multiple bilobar CLM received a OSH at the Humanitas Research Hospital, Rozzano, Italy (HRH). Four with simultaneous extra-hepatic distant metastases were excluded, while no patient had intraoperative radiofrequency ablation of CLM. Finally, 89 patients were retained.

The 83 TSH patients of PBH (cases) and the 89 OSH patients of HRH (controls) were matched according to the most relevant prognostic factors described in the literature,<sup>18,19</sup> including N status of the primary tumor (N0/N+); timing of CLM diagnosis (synchronous/metachronous); CLM number (<8/8–10/>10); and distribution of nodules into the right and the left liver. Preoperative imaging of all patients was reviewed to assess the number of CLM and their position into the liver. Twenty patients of the TSH group and 26 of the OSH group were excluded because no matching was possible, i.e., no patient with adequate similar characteristics in the other group was available. Finally, 63 TSH patients from the PBH were compared with 63 OSH patients from the HRH in a case-control setting. The study was approved by the local ethics committees.

## The two approaches

Both TSH and OSH have been previously described.<sup>3,17</sup>

Briefly, the OSH approach schedules the removal of all the multiple bilobar CLM in a single LR, even in presence of deep-located metastases. Developed by the HRH group, it relies on: the extensive use of intraoperative ultrasonography for staging and resection guidance; CLM-vessel detachment whenever possible; communicating vessels detection among hepatic veins for preserving parenchyma despite sectioning the main draining vein. The combination of these techniques allowed minimizing the need for major hepatectomies and for TSH.

The TSH has been proposed and developed by the PBH group.<sup>3</sup> It scheduled: 1) the extirpation of lesions in the planned FLR, during the first operation; 2) the PVO; 3) the major hepatectomy, at least four weeks later, provided an adequate FLR hypertrophy. An interval chemotherapy was administered in the majority of patients. In case of disease progression at restaging (with or without interval chemotherapy) a new chemotherapy line was scheduled.

## Patients' management

The patients' management in the two centers was similar. All patients were staged according to thoraco-abdominal computed tomography (CT), hepatic magnetic resonance imaging (MRI) and positron emission tomography (PET)-CT.

A multidisciplinary oncologic committee evaluated each patient. Preoperative (conversion or neoadjuvant) chemotherapy was systematically considered. Patients were restaged after a short chemotherapy (4–6 cycles) and surgery was scheduled in case of tumor response or stabilization. Patients showing disease progression were scheduled for a second line treatment; exceptionally, surgery was planned despite progression after multidisciplinary consensus, mainly in the early years of the present series. Immediate surgery without preoperative chemotherapy was scheduled in the first years of the present series, in patients with tiny lesions at risk of disappearance, and in patients with intraoperative detection of additional CLM.

Adjuvant chemotherapy was evaluated on a case-by-case basis at the HRH due to the absence of consensus in the literature on this subject, while it was systematically scheduled at the PBH. Follow-up of all patients was performed every three months and included Carcinoembryonic Antigen (CEA) levels and abdominal ultrasonography, thoraco-abdominal CT or hepatic MRI.

## Definitions

Synchronous CLM were considered those diagnosed  $\leq 3$  months after the colorectal tumor diagnosis. Major hepatectomy was defined as the resection of  $\geq 3$  Couinaud adjacent segments. CLM were defined as having a major vascular

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