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Original article

# Preliminary experience in anesthetic management of patients undergoing auxiliary liver transplant according to the RAPID procedure

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ABSTRACT

*Background:* RAPID (Resection And Partial Liver Transplantation With Delayed Total Hepatectomy) is a novel two-stage surgical procedure, with only 23 reported cases, involving partial liver resection and transplantation of a left lobe (stage 1) followed by a delayed total hepatectomy (stage 2). The perioperative anesthetic management of these recipients presents unique challenges and has never been described so far.

*Materials and methods:* We report on ten patients with unresectable liver metastases who underwent this procedure from a living donor in our center between May 2020 and April 2024. Retrospectively, we collected preoperative, graft-related, and intraoperative management data during stage 1 (S1) and stage 2 (S2), and postoperative outcomes.

*Results and discussion:* Recipients' median age was 53 (50–57), median graft-to-recipient weight ratio 0.43 % (0.41–0.45), total ischemia time 82 min (75–105). No patients experienced postreperfusion syndrome. Median intensive care unit (ICU) stay was 36 h (27–48) after S1, 24 h (24–48) after S2. Median INR on POD 3 was 1.20 (1.13–1.29) after S1, 1.29 (1.16–1.70) after S2. Complications after S1 included portal thrombosis in one patient, and three required revision surgery. After S2, one patient required revision for hemostasis, and another developed acute kidney injury. This patient died on day 12 from bleeding post-thoracocentesis for pleural effusion. Six-month survival rate was 90 %.

*Conclusions:* These preliminary data, as a first step in developing perioperative management protocols for this innovative surgery, show good hemodynamic tolerance, no postreperfusion syndrome, and preserved liver function throughout the process. These results highlight the RAPID procedure's safety during surgery and postoperative course.

**Key points summary**

Question: What are the preliminary data on anesthetic management of patients undergoing auxiliary liver transplant according to the RAPID procedure?

Finding: Our preliminary data show good hemodynamic tolerance, no postreperfusion syndrome, and preserved liver function throughout the process despite the use of very small grafts.

Meaning: We emphasize the anesthetic stability and the safety of the RAPID technique for the recipients.

## Introduction

The living donor RAPID procedure (Resection And Partial Liver Transplantation With Delayed Total Hepatectomy) represents an innovative two-stage transplantation technique. The first stage (S1) includes a recipient left hepatectomy (encompassing segments II, III, and IV) and the orthotopic implantation of a left graft (segments II and III) from living donation. The native right liver is deportalized by ligating the right portal pedicle. Redirecting the entire portal flow towards the graft

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stimulates regeneration and allows for a rapid volumetric increase of the graft, enabling the residual right completion hepatectomy, i.e., the second stage (S2), within 15 days.

It offers a potential curative treatment for patients with non-resectable liver cancer in non-cirrhotic conditions and presents several significant advantages. Firstly, this procedure does not increase the demand for the cadaveric organ pool. Secondly, it reduces donor morbidity by necessitating only a minor resection from the living donor. Notably, a left-sided donation is considerably safer than the more commonly required right-sided liver donation for adults. The auxiliary graft technique also provides a valuable hepatic metabolic safeguard to the recipient in case of graft dysfunction because it leaves the recipient's right liver in place until the graft reaches sufficient volume and function [1–5].

Despite these advantages, the adoption of this two-step procedure remains limited due to its technical complexity and potential impact on early surgical outcomes. However, refinements in surgical techniques are continuously evolving and are being increasingly well-documented [3,5].

Currently, there are no anesthesia guidelines for managing patients undergoing these procedures, though developments are expected in the future. From May 2020 to April 2024, our transplant center performed two-stage liver transplantations using left (-lateral) segments from living donors on ten patients with unresectable colorectal or neuroendocrine liver metastases.

This report details our preliminary experiences and discusses the specific anesthetic implications, which significantly differ from those associated with conventional hepatectomy or orthotopic liver transplantation (OLT).

## Methods

The local ethical committee approved the surgical procedure (CEHF 2020/19FEV105). Written informed consent was obtained for all patients. Our transplant center participates in the prospective multicenter study registered at ClinicalTrials.gov (NCT04865471). All recipients underwent comprehensive preoperative evaluations, including electrocardiography, echocardiography, pulmonary function tests, and a psychological examination. Hepatic biliary and vascular anatomy were assessed by magnetic resonance imaging (MRI) and computed tomography (CT). Liver volumes and graft-to-recipient weight ratios (GRWR) were estimated based on MRI and CT imaging. All procedures were performed by a single surgeon (LC).

Intraoperatively, a large-bore peripheral intravenous catheter, a radial arterial catheter, and a central venous catheter were placed in all recipients for both stages. Patients were additionally monitored with cerebral near-infrared spectroscopy (NIRS) and processed electroencephalography (Neurosense®). For both S1 and S2, the anesthesia induction protocol included a low dose of sufentanil (0.1 μg $kg^{-1}$), lidocaine 1 mg $kg^{-1}$, propofol adapted to depth of anesthesia monitoring (Neurosense®), ketamine 0.5 mg $kg^{-1}$, and rocuronium 0.5 mg $kg^{-1}$. Maintenance of anesthesia was assured by propofol or sevoflurane according to the senior anesthetist's preference. Administration of fluids was individualized according to the principles of goal-directed fluid therapy. During S1, hydrocortisone 200 mg was administered at induction and the end of the procedure according to our institutional immunosuppressive protocol for OLT. Mannitol 600 mg $kg^{-1}$ was given before unclamping. The postoperative analgesia strategy was developed case-by-case in consultation with the senior anesthesiologist, the surgeon, and the patient.

We retrospectively collected the data from the patients who underwent this intervention in our transplant center. The recorded parameters were the following: indication for transplantation, the interval between the two stages, GRWR, ischemia times, liver function tests, and recipient outcomes. For S1 and S2, we collected the following data: intraoperative blood loss, arterial blood gas analysis values, fluid management strategy and diuresis, analgesic techniques, and postoperative pain scores until the postoperative day (POD) 3. We also referred to the composite outcome generally used to define early allograft dysfunction (EAD) by the presence of at least one of these criteria: peak ASAT or ALAT $\geq$ 2000 U $L^{-1}$ during the first week, total bilirubin $\geq$ 10 mg $dl^{-1}$ or INR $\geq$ 1.6 at POD 7 [6]. We assessed the morbidity and mortality of these patients during the first six months post-operatively using the Clavien-Dindo classification. Data are presented as descriptive statistics using Prism software version 10.2.2.

## Results

Preoperative data are presented in Table 1. Indication for surgery was unresectable colorectal tumor metastases in seven patients and unresectable neuroendocrine tumor metastases in three patients. None of the patients presented with cirrhosis or portal hypertension. Preoperative INR was normal ($\leq$ 1.2) in all patients before S1.

The fluid strategy was based on the administration of balanced crystalloid solutions, with the addition of colloids in some cases. Two patients required transfusion at S1, of one and two units of packed red blood cells (PRBCs), respectively. At S2, three patients were transfused. They received one or two PRBCs (Table 2). Median graft weight was 326 g (272 – 361), and initial median graft-to-recipient weight ratio at S1 was 0.43 % (0.41 – 0.45) (Table 3). No patient experienced post-reperfusion syndrome.

All patients could be extubated immediately after the procedure following both S1 and S2, except one patient after S1 because of the long duration of the intervention (1091 min).

Various approaches were utilized to manage pain both during and after surgery for different patients. During both S1 and S2, intrathecal morphine (3 μg $kg^{-1}$) was administered to four patients, and one patient received a TAP block. Another patient benefited from TEA during S1. Five patients received ketorolac (30 mg) during S1, and five patients during S2. A patient-controlled intravenous morphine pump was used in all patients after both stages as rescue analgesia.

Table 3 presents graft data. Maintenance of anesthesia was ensured with sevoflurane in all recipients. One recipient developed EAD after S1 and S2, with subsequent favorable evolution. Another patient presented EAD only after S1. Figs. 1 and 2 show the postoperative evolution of INR and renal function. One patient developed postoperative renal failure (KDIGO 2) on POD 3 after S2. Figs. 3 and 4 show the postoperative Numeric Rating Scale (NRS), respectively at rest and during movement after both stages. The time between S1 and S2 was 16 (14–16) days. The median length of stay in ICU was 36 h (27–48) after S1 and 24 h (24–48) after S2, with an overall hospital stay of 24 days (18–27).

The evaluation of surgical complications, using the Clavien-Dindo classification, is shown in Fig. 5. Patient 2 developed portal thrombosis on POD 15 after S1, requiring treatment with low-molecular-weight heparin (LMWH) and was subsequently postponed. Patient 3

**Table 1**
Preoperative data.

| | Recipients (N = 10) |
|---|---|
| Age (years) | 53,5 (50 – 56,7) |
| Gender | |
| Male | 7 |
| Female | 3 |
| BMI | 23,6 (22,1 – 26,9) |
| Origin of unresectable liver metastasis | |
| Colorectal | 7 |
| Neuroendocrine | 3 |
| Biological data | |
| INR | 1,05 (1,01 – 1,12) |
| Hemoglobin (g/dL) | 12,7 (12,0 – 13,6) |
| Creatinin (mg/dL) | 0,90 (0,69 – 0,99) |
| Bilirubin (mg/dL) | 0,65 (0,35 – 0,87) |

Data are expressed in Median (P25 – P75) or in Numbers.

**Table 2**
Intraoperative data.

| | Stage 1 (S1) | Stage 2 (S2) |
|---|---|---|
| Duration of surgery (min) | 674 (613 – 722) | 133 (106 – 167) |
| Lactate peak (mmol/L) | 4,8 (3,2 – 5,8) | 1,4 (1,1 – 1,5) |
| Blood loss (mL) | 725 (462 – 900) | 100 (50 – 145) |
| Red Blood Cells transfused (mL) | 0 (0 – 0) | 0 (0 – 205) |
| Crystalloids (mL) | 4250 (3500 – 5375) | 1000 (500 – 1000) |
| Colloids (Albumin 5 %) (mL) | 650 (125 – 1000) | 0 (0 – 0) |
| Diuresis (mL $kg^{-1}$ $h^{-1}$) | 1,43 (1,08 – 1,99) | 1,37 (0,66 – 2,32) |
| Norepinephrine max (µg $kg^{-1}$ $min^{-1}$) | 0,09 (0,07 – 0,1) | 0,03 (0,00 – 0,05) |

Data are expressed in Median (P25 – P75).

**Table 3**
Graft related data.

| | Stage 1 (S1) |
|---|---|
| Total ischemia time (min) | 82 (75 – 105) |
| Graft weight (g) | 327 (272 – 361) |
| Graft to body weight ratio (%) | 0,43 (0,41 – 0,45) |

Data are expressed in Median (P25 – P75).

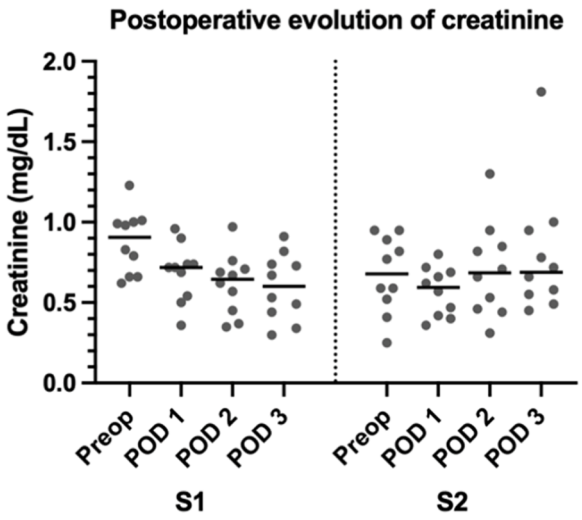


**Fig. 2.** Postoperative evolution of serum creatinine.
Data are presented as dots (each dot represents a patient) and Median.

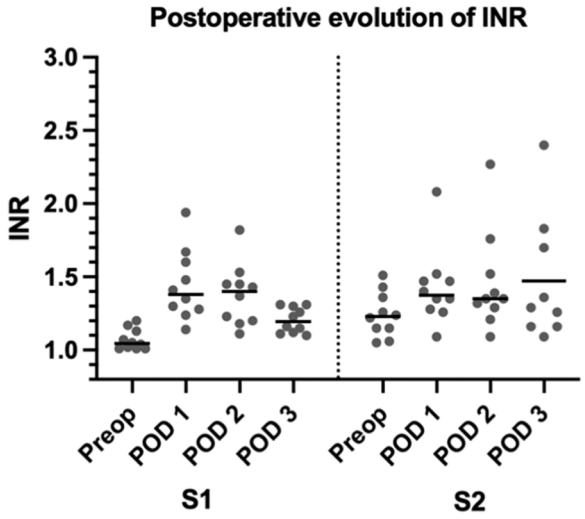


**Fig. 1.** Postoperative evolution of INR.
Data are presented as dots (each dot represents a patient) and Median.

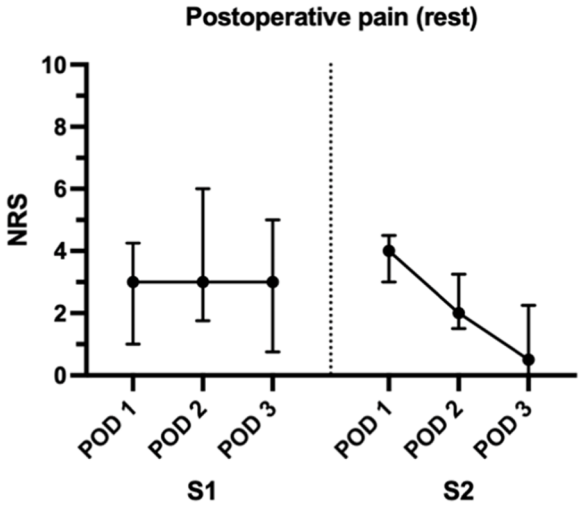


**Fig. 3.** Postoperative pain at rest.
Data are presented as Median with interquartile range.

suffered arterial bleeding at the jejunal anastomosis on POD 11 after S1, requiring surgery for hemostasis. Completion hepatectomy was performed at the same time. Patient 4 developed active arterial bleeding at the stump of the hepatic artery on POD 2 after S2, necessitating revision surgery. Patient 4 suffered a digestive hemorrhage with melena exteriorization on POD 12 after S1, which resolved spontaneously. During S2, biliary peritonitis localized around the right liver was demonstrated in the same patient. Patient 5 developed sepsis on POD 13 after S1, requiring surgical exploration. A right biliary leak was identified, and the completion hepatectomy was performed at the same operative time. The patient died on POD 20 of a massive hemothorax after percutaneous drainage of a secondary pleural effusion.

## Discussion

### *Hemodynamics*

#### *Vascular clamping*

Pedicle clamping using the Pringle maneuver was not necessary during the resection of the metastatic left liver in our recipients. We have developed a progressive dissection technique using CUSA® and bipolar forceps, which rarely requires occlusion of the hepatic pedicle during even complex liver resection. We routinely resected the main portal vein bifurcation during S1. This technique allows us to align the traction lines of the portal tripod, thereby avoiding secondary kinking that we would have encountered with an anastomosis between the two left portal veins. The reconstruction of the graft outflow is anatomical; common trunk (left and middle hepatic veins) of the donor on the common trunk of the recipient by a termino-terminal anastomosis under selective clamping, leaving the inferior vena cava of the recipient completely free during implantation.

The hepatic manipulations inherent to the progression of the surgical dissection may partially impair the venous return, as is common in hepatic surgery. There is no anhepatic phase, and the duration of portal clamping is shortened: the right portal vein is left connected to the residual right liver while the graft outflow is reconstructed. This is a major difference from standard living donor liver transplantation. Splanchnic venous stasis is, therefore, significantly shorter compared to OLT. Similarly, unlike OLT, the RAPID procedure does not require clamping of the inferior vena cava. The hemodynamic consequences are, therefore, moderate and well tolerated. During S2, right hepatectomy is classically performed by clamping the right portal vein, which had

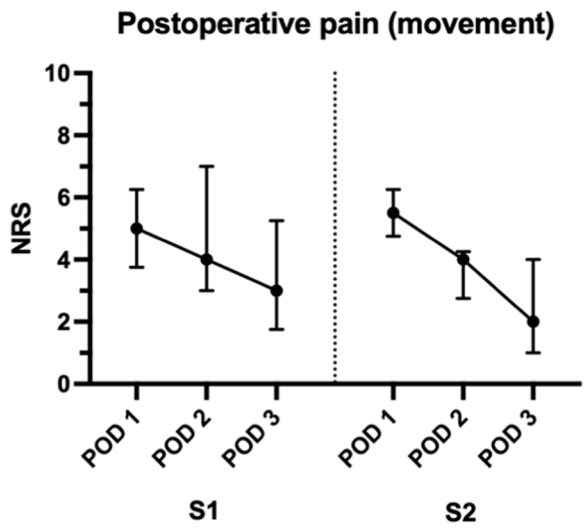


**Fig. 4.** Postoperative pain with movement.
Data are presented as Median with interquartile range.

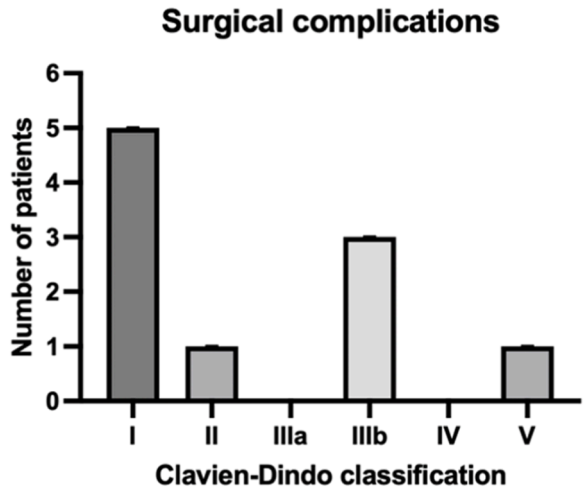


**Fig. 5.** Surgical complications.
Data are presented as Numbers of patients.

previously been ligated during S1, and the right hepatic vein. At S2, hepatic inflow and outflow are always preserved through the left graft.

It should be noted that, although this type of surgical procedure has already been described in patients with end-stage liver disease [7], all the patients we managed had an oncological indication for transplantation and did not suffer from cirrhosis or portal hypertension.

*Reperfusion syndrome*

Reperfusion syndrome, defined as a drop in mean arterial pressure of 30 % of its baseline value for at least one minute during the five minutes following unclamping, is a frequent complication in liver transplantation [8]. Its occurrence is associated with an increased incidence of postoperative complications such as EAD or primary graft non-function. This syndrome is also associated with increased postoperative morbidity and mortality, as well as a higher risk of graft loss at three months [9]. The mechanisms involved are complex and are currently only partially understood. During unclamping, the abrupt hypotension is attributed to the sudden inflow into the systemic circulation of endotoxins, reactive oxygen derivatives species, vasoactive, hyperkalemic, cold, and acidic substances from a mixture of the preservative solution, graft, and recipient's ischemic intestine [10]. Its occurrence in liver transplantation is around 30 %, both after cadaveric and living donation [10,11]. Our cohort did not observe a reperfusion syndrome in any patient. Although the small number of cases does not allow generalization, the smaller hepatic volume and the lower blood volume involved in the reperfusion of an auxiliary graft could partly explain the attenuation of this syndrome in our cohort. Moreover, the mesenteric venous return is interrupted only briefly and continues to flow through the right portal branch during most of the graft implantation.

*Blood loss and transfusion*

Transfusion requirements for both stages were low in our patients. At S1, this can be explained by the absence of portal hypertension and coagulopathy, both frequently encountered in patients with cirrhosis awaiting OLT and associated with blood loss during OLT. Moreover, relative hemodynamic stability encountered in the RAPID procedure compared to OLT could reduce acidosis and dilutional coagulopathy, further reducing blood loss. However, the RAPID procedure requires parenchymal transection at S1, which could increase bleeding during dissection and reperfusion when compared to the "en bloc" total hepatectomy of OLT. At the end of S1, the surgeon placed a silicone sheet between the graft and the native right liver, thus limiting postoperative adhesions and reducing blood loss at S2.

*Metabolic considerations*

The metabolic abnormalities usually encountered during the anhepatic phase in OLT do not occur during S1, as the inflow and outflow through the right liver are maintained during most of the procedure. Ligation of the right portal vein at the end of S1 has little metabolic repercussions as arterial inflow is maintained in the remnant right liver. Similarly, the early graft function, usually assessed intraoperatively by the decrease in lactatemia and the occurrence of hyperglycemia during the neohepatic phase, cannot be evaluated by these indicators in this case.

Graft size is a known predictive factor of graft dysfunction. Recipients of grafts $< 1$ % GRWR are at risk of developing small-for-size syndrome [12]. One of the main advantages of the RAPID procedure is that it allows the use of small grafts because the recipient's right remnant liver serves as a metabolic backup. After S2, two patients presented criteria compatible with the definition of EAD. Biological parameters of liver function stayed normal in the other patients despite low initial GRWRs.

*Pain management*

Pain experienced by patients undergoing OLT is usually low, even without locoregional analgesic techniques such as epidural or abdominal wall blocks [13,14]. In contrast, patients undergoing open liver resection typically report severe pain, even with effective epidural analgesia [15]. No study has yet been conducted on postoperative pain after an auxiliary liver transplant according to the RAPID procedure. Furthermore, the implications of performing two liver surgeries in a short period are unknown in terms of postoperative pain.

In our cohort, these S1 and S2 interventions are associated with moderate to severe postoperative pain on mobilization, with important interindividual variations. This may be inherent to the procedure itself and the absence of a well-defined analgesic protocol in our institution for this new type of surgery.

The use of thoracic epidural analgesia (TEA) has been successfully described for OLT in patients without contraindications (INR $< 1.5$ and platelets $> 100{,}000/mm^3$) [13]. Considering the safety offered by the right liver remaining as a functional backup, it may be legitimate to discuss the placement of TEA during S1. Given the hypertrophy of the graft, which ensures a satisfactory liver function, TEA could also be considered for S2 when surgery is performed through an open approach.

This should be discussed on a case-by-case basis.

A bilateral subcostal TAP block performed at the end of the procedure could also be a safe and effective locoregional analgesic option for both S1 and S2. The ESRA recommendations propose this option after open liver resection as a possible alternative to TEA [16]. Furthermore, a before-and-after study has recently demonstrated the interest of TAP block in decreasing opioid consumption after OLT [14]. Future studies should investigate the efficacy and safety of performing an intrathecal injection of morphine at the beginning of the procedure.

In our cohort, one patient (patient 4) developed AKI on POD 3 after S2. While NSAIDs are commonly used intra- and postoperatively in open liver resection, their intraoperative administration in liver transplantation is usually not generalized due to concerns about their renal toxicity. The administration of calcineurin inhibitors may reinforce these concerns, as they are used as standard immunosuppressive agents to prevent graft rejection, a drug class also known to be nephrotoxic. However, it should be noted that only mild immunosuppression with tacrolimus was used in our cohort, and the dogma is currently being questioned. Indeed, Chen et al. demonstrated the safe perioperative use of ketorolac in children receiving a liver transplant [17]. In the RAPID procedure, anti-inflammatory drugs could be considered more systematically because hemodynamic changes are less pronounced than in OLT.

*Oncoanesthesia*

Furthermore, although surgical resection remains a cornerstone of curative cancer treatment, it paradoxically represents a high-risk period for cancer progression. Surgery can trigger the release of additional circulating tumor cells which may travel to distant sites and initiate micrometastases [18]. This phenomenon may be associated with increased vascularity driven by amplified angiogenic factors and immune suppression, influenced by pain and neural activation [19]. Moreover, surgical stress triggers local and systemic inflammation, creating an environment rich in inflammatory molecules more likely to be colonized by circulating tumor cells, increasing the risk of recurrence [20]. The intraoperative administration of NSAIDs is a simple and effective approach that can be integrated into the anesthetic regimen to mitigate the surgical stress response. Different epidemiological studies have shown that long-term NSAIDs use is associated with a reduction in cancer incidence [21,22]. COX-2 expression is dysregulated in many types of cancer and is closely linked to key processes such as carcinogenesis, tumor invasiveness, and angiogenesis [23]. A recent systematic review and meta-analysis have shown that intraoperative administration of NSAIDs during oncological surgery is associated with improved overall and recurrence-free survival [19]. Indeed, these drugs interfere with the immune response against circulating tumor cells during surgical resection of solid tumors. Some NSAIDs appear to offer more significant benefits than others in this context. Ketorolac is particularly interesting due to its R-enantiomer, which inhibits specific GTPases that play a crucial role in metastatic processes [24]. The beneficial effect of intraoperative ketorolac may also be attributed to its lower immunosuppressive impact than other analgesics [25]. The administration of ketorolac during S1 and S2 of the RAPID procedure could thus benefit oncological outcomes, but this hypothesis needs to be demonstrated by further studies. Indeed, its efficacy could depend on the tumor type, and extrapolating the specific case of liver metastases should remain cautious as long as the molecular and cellular mechanisms have only partially been elucidated.

*Limits and perspectives*

This retrospective single-center study, presenting our preliminary experience with the anesthetic management of patients undergoing this innovative surgical procedure, is the first to be reported in the literature. However, it has several significant limitations. First, our observations are based on a limited cohort of ten patients, which restricts their generalizability. Second, postoperative analgesic strategies varied considerably depending on the senior anesthetists in charge. This variability reflects the lack of established guidelines and highlights the need for standardized analgesic protocols tailored to the specific context of auxiliary liver transplantation. Finally, given the novelty of this type of surgery, we acknowledge the limited long-term follow-up available on the evolution of these patients. Further prospective multicenter studies with larger cohorts are required to complete these preliminary results. These studies should focus on optimizing perioperative management as well as long-term outcomes, including graft function, patient quality of life, and overall survival.

## Conclusion

This new surgical technique invites us to reconsider our practices and change our paradigm. The RAPID procedure is not just a classical open liver resection with the bonus of an additional liver graft, nor a classical liver transplant with the bonus of a remaining right liver followed by a completion hepatectomy. Our preliminary data show good hemodynamic tolerance, no postreperfusion syndrome, and preserved liver function throughout the process despite the use of very small grafts.

Otherwise, the contribution of new findings in oncoanesthesia, a discipline still in its early stages, will be crucial for managing these recipients. In the coming years, studies specifically focused on the particular case of the RAPID procedure will be needed to develop new anesthetic protocols, ensuring optimal care for patients benefiting from this innovative surgery. Our center has already emphasized the twofold safety of the RAPID technique: first, for the donor, who undergoes a standardized left hepatic resection, and second, for the recipient, who is protected from graft dysfunction by the presence of a residual right liver. We moreover emphasize the anesthetic stability of the recipients.

## Financial disclosure

None.

## CRediT authorship contribution statement

**Marie-Hélène Lagios:** Writing – original draft, Methodology, Conceptualization. **Audrey Dieu:** Writing – original draft, Methodology, Conceptualization. **Loïc Benoit:** Writing – original draft, Methodology, Conceptualization. **Arnaud Steyaert:** Writing – review & editing, Methodology. **Virginie Montiel:** Writing – review & editing. **Aude Vanbuggenhout:** Project administration. **Lancelot Marique:** Writing – review & editing. **Laurent Coubeau:** Writing – review & editing, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.liver.2025.100268.

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