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Resection and partial liver transplantation from deceased donors with delayed total hepatectomy (RAPID procedure) for hepatocellular carcinoma: a national, multicenter, non-randomized, prospective trial

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Abstract

Background This trial wants to ascertain whether the RAPID procedure could improve graft availability and patient survival in hepatocellular carcinoma (HCC) setting. RAPID-HCC trial, which aims to decrease waiting times and mortality for patients on the transplant list by adopting a novel surgical approach, could be a major step forward in liver transplantation (LT). If successful, the RAPID procedure could become a new standard of care for LT, addressing the critical shortage of organs and improving outcomes for selected patients with early-stage HCC. We expected to provide critical evidence to support the wider adoption of this new approach.

Methods The RAPID-HCC trial is a prospective, multicentre study conducted across five major university hospitals in France aiming to assess the feasibility, safety, tolerance, and efficacy of the RAPID procedure on HCC patients. A total of 50 adult HCC patients with preserved liver function (MELD score ≤ 15) will be enrolled and 34 of these will receive a split liver graft from a brain-dead donor (DBD). The RAPID procedure consists in splitting a deceased donor liver and transplanting it into two adult recipients. The operation consists of two phases: first, the donor's left lateral lobe (G23) replaces the recipient's left liver lobe (H1234), while the native right lobe stays to support hepatic function. The recipient's right lobe (H5678) is removed four months later, leaving the graft fully functional. Primary outcomes will focus on the feasibility and safety of the procedure, assessed by successful completion of both surgical stages and monitoring for adverse events. Secondary outcomes will include graft and patient survival, incidence of rejection and HCC recurrence, waiting times and overall patient outcomes compared to conventional whole liver transplantation.

Discussion Early insights from several studies hint that the RAPID method might improve graft availability and recipient survival. Still, further studies are needed to confirm these benefits, especially for HCC patients.

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RAPID HCC trial pushes forward liver transplants for HCC patients who still have good liver function. This method could reduce waiting times and mortality in transplant candidates. If successful, the RAPID procedure could be adopted as a new standard for LT.

Trial registration {2a} {2b} ClinicalTrials.gov NCT05971628. Registered on August 2, 2023, before the start of inclusion.

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Keywords Partial liver transplantation, Auxiliary liver transplantation, HCC, Graft split, Two stages hepatectomy, Delayed hepatectomy

Introduction

Background and rationale {6a}

Hepatocellular carcinoma (HCC) represents the sixth most common cancer globally and is the most prevalent primary liver tumour, with more than 8,000 new cases diagnosed annually in France. In 90% of cases, HCC develops in the context of fibrosis/cirrhosis parenchyma [1]. Curative treatments include liver resection, liver transplantation (LT), and local destruction. No chemotherapy has been demonstrated to be an effective curative treatment. LT is an optimal treatment for HCC as it addresses both the tumour and the underlying liver disease, the primary risk factor for HCC. Extensive literature comparing resection with LT concludes that LT is the optimal treatment despite initial morbidity and mortality risks. However, organ shortages prevent universal availability of LT for HCC [2]. Current recommendations advocate LT for all patients with one or more HCCs (BCLC stage A) who are non-surgical candidates due to severe liver failure or portal hypertension [3, 4]. HCC is the primary indication for LT in France; however, HCC patients frequently lack liver insufficiency, which constrains access to LT despite specific allocations. In these cases, the mean waiting time for LT is 12–18 months, with a delisting rate of 15–20% due to tumour progression or death [5], and only 66% of listed patients receive a transplant within two years. Improving access to transplantation is imperative, but limited by organ shortage. Shortening the LT waitlist for HCC has been debated due to concerns about reduced recipient selection and potential risk of relapse. However, the consensus is that there is no increased risk despite "selection by time". A comparison of deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT) found similar recurrence and survival rates, with the shorter waiting time of LDLT, preventing patient dropout [6]. A meta-analysis supports these findings and suggests that shorter waiting times and alternative strategies improve organ availability [7].

The RAPID LT technique has been already described and consists of an auxiliary LT with a staged hepatectomy, specifically designed for this purpose. This strategy gives rapid access to a graft offered to a prioritized recipient at the top of the list.

Liver shortage is a global challenge that requires new alternatives to increase the supply of organs. In France, Europe and the USA [8], adult LT mainly uses whole grafts from Brain Dead Donors (DBDs). In Asia and the Mediterranean region, however, partial grafts are more common, often from living donors [9, 10]. In Europe, partial LT is rare but possible with LDLT or split cadaveric grafts [11, 12]. Splitting a whole graft to create two partial liver grafts effectively increases the number of organs available [13] and is commonly used in paediatric transplantation. However, left lateral lobe transplantation in adults is associated with high complication rates, leading to its abandonment in France. Conversely, right liver transplants (G45678) in adults have survival rates comparable to whole organ transplants [14, 15]. Splitting an organ for transplantation in two adults (i.e. right [G5678]/left [G1234] livers) could theoretically almost double the number of transplants but this procedure is often limited by donor morbidity and anatomical contraindications regarding right-sided graft [16]. Secondly, European results of left split LT remain disappointing with high risk of small-for-size-syndrome [17, 18], thus limiting enthusiasm for LT with left livers. Supportive partial auxiliary LT has the potential to expand the organ pool without the risk of liver failure. Despite the technical challenges, recent advances have led to improved outcomes and there have been reports of excellent patient and graft survival rates in patients with chronic liver disease who have undergone auxiliary partial allografts [19–22].

The RAPID-HCC trial aims to evaluate the feasibility, as well as the outcomes and the graft "gain" of a standardized RAPID procedure using a small graft from a split whole deceased donor graft. The RAPID procedure has been applied to primary or secondary liver tumors,

with ongoing European trials in metastatic liver disease (NCT02215889 and NCT03488953) (https://trialfinder.panfoundation.org/en-US/trial/listing/87796) [23]. Approximately ten published RAPID cases [24–30] showed successful partial hepatectomy and left partial accessory graft transplantation, followed by complete hepatectomy of the native liver after an average of three weeks. Mid-term results were excellent with no small for size syndrome or increased risk of cancer recurrence. The literature also reports 27 orthotopic liver transplants in patients with chronic liver disease ± HCC, supporting the RAPID procedure [20]. Notably, our team was the first to report this protocol in a cirrhotic patient [13]. This multicentre study aims to address the challenges of LT in HCC patients with an innovative surgical technique.

Objectives {7}

We aim to assess the clinical feasibility, tolerability, outcomes and overall graft gain via the implementation of a standardized RAPID procedure in HCC patients. Key objectives will evaluate the procedural feasibility of graft splitting, including both technical aspects and logistical challenges. Tolerability will be assessed by monitoring the recipient's ability to tolerate the surgical procedure and the immediate post-operative period without significant adverse events. Clinical outcomes will be measured by graft function, patient survival and complication rates with a focus on small for size syndrome, graft dysfunction and vascular or biliary complications. In addition, the study will quantify the increase in transplantable organ availability. By splitting a single liver graft for two recipients, this procedure could alleviate the organ shortage crisis and potentially double transplantation capacity. The results of the RAPID-HCC trial will be compared to standard LT using whole grafts, focusing on survival, graft function and overall patient health. The RAPID HCC trial is hypothesized to demonstrate comparable clinical outcomes, increase organ availability, reduce patient dropout and improve survival.

Trial design {8}

The RAPID-HCC trial (Resection and partial liver transplantation with delayed total hepatectomy for Hepatocellular Carcinoma) has been designed as a national, multicentric, non-randomized, prospective trial evaluating the feasibility and the tolerance of the RAPID procedure in HCC patients (with preserved liver function) requiring a liver transplantation.

Study setting {9}

The study will be conducted across five France transplantation centers. With the final objective of performing the RAPID procedure on 34 patients, the RAPID-HCC trial will enroll 50 patients with HCC with preserved liver function but requiring LT according to the usual transplant criteria. The trial's maximum duration is 70 months, comprising a 24-month enrollment period, a 6-month interval between selection and enrollment, up to 12 months from enrollment to the first RAPID stage, a maximum 4-months between the two RAPID steps, and a 24-month patient follow-up period after the second RAPID stage.

Eligibility criteria {10}

Eligibility criteria will concern the donors and the recipients.

Donor selection criteria

- Brain-dead donor
- Age: 18 to 65 years
- Hepatic vascular and biliary anatomy compatible with performing a split. The analysis, based on the donor's CT scan, will be provided by the team responsible for executing the split.
- Biological and hepatic profile compatible with performing a split, specifically transaminases < 4 times the normal level
- Graft not assigned to a protocol requiring machine perfusion
- Serologies: Anti-HBc and anti-HCV antibodies negative

Recipient selection criteria (RAPID Recipient)

- Age: 18 to 68 years
- Indication for LT for HCC validated in a multidisciplinary meeting
- AFP score ≤ 2 [15, 31]
- Body mass index (BMI) < 30 kg/m.^{2}
- MELD score ≤ 15, without access to prioritization
- PET CT-choline and PET CT-FDG, or MRI, showing no signs of extra-hepatic oncologic disease, deemed significantly at risk by the Scientific Committee
- Patient informed and able to provide written consent to participate in the RAPID-HCC study
- Affiliation to the French national social security system
- Validation of the patient's inclusion in the RAPID-HCC protocol by the scientific committee

Recipient exclusion criteria

- History of liver transplantation, surgical or radiological portocaval anastomosis (TIPS)
- History of major abdominal surgery (including hepatectomy)

- History of abdominal extra-hepatic radiotherapy
- History of acute or chronic pancreatitis
- Expected combined transplantation
- HCC located at a distance ≤1 cm from the transection line required by the first-stage hepatectomy
- Portal or arterial thrombosis
- Pre-transplant portocaval gradient ≥20 mmHg
- Presence of more than one HCC lesion in the right liver requiring partial hepatectomy during the first-stage surgery
- Hepatectomy in the future remaining liver involving a resected volume greater than one hepatic segment
- Presence of ascites (clinical or radiological) within the past 5 years, considered at risk by the Scientific Committee
- Positive hepatitis C viral load
- Acute or chronic active hepatitis B (HBs antigen detected by serology)
- Positive HIV serology
- Severe comorbidities, particularly severe cardiovascular, respiratory, or renal pathology (at the discretion of the medical-surgical team)
- Patient on anticoagulant therapy
- Ongoing mechanical ventilation
- Patient requiring inotropic support
- Highly sensitized recipient
- Patient who has received (or is expected to receive) preoperative treatment with radioembolization of the right side, hepatectomy, or radiotherapy near the hilum
- Patient who has received (or is expected to receive) preoperative treatment with tyrosine kinase inhibitors (TKI) within the last three months
- Patients receiving or having received immunotherapy
- Adults under legal protection measures (guardianship, curatorship, or judicial protection)
- Patients deprived of liberty by judicial or administrative decision
- Pregnant or breastfeeding women
- Psychological or psychiatric disorders that would compromise proper follow-up

Interventions

Explanation for the choice of comparators {6b}

The standard French liver allocation policy will be followed. In accordance with an agreement with the Agence de Biomédecine (France), recipients of RAPID will be accorded priority status (800 points at six months), thereby ensuring their expedited access to LT. The control group comprises patients listed for HCC with the same matching criteria as the experimental arm, during the same time period as the study, in all French liver transplant centers, and in active status (not temporarily contra-indicated). Group matching will be based on date of listing (± 6 months), sex, age (≤ 50/> 50 years), alpha-fetoprotein level (≤ 100/> 100 µmol/L), underlying liver disease (alcohol, viral, metabolic, other), pre-transplant treatment (yes/no, regardless of type) and MELD score (≤ 11/> 11). Matching will be performed to optimize the number of control patients analyzed (from 1 RAPID/1 control to 1 RAPID/4 controls). These data will be made available by the ABM at the end of the study. A second matching will be performed between RAPID patients and control patients who have undergone liver transplantation. The groups will be matched using the same criteria as the previous matching. This matching will be used to compare two-year post-transplant survival between the groups.

Intervention description {11a}

The RAPID-HCC trial is a prospective, multicentric study investigating an innovative approach to LT. Two adult recipients will be transplanted with split grafts from a deceased donor. The right-sided graft recipient is excluded from the study because extensive experience in pediatric LT sharing showed that right lobe transplants have comparable outcomes to whole liver transplants [15, 16]. This study will focus on left lateral lobe (G23) recipients with one or more HCCs and preserved liver function. Optimizing the logistics of procurement, splitting and transport to minimize cold ischaemia time for both grafts is critical. All participating centers are committed to reducing cold ischemia time, with an 8-h limit as a target but not an exclusion criterion. Donors located far from the transplant site and accessible only by air will be included, but longer cold ischaemia times will need to be considered. The teams will assess these logistical parameters when accepting or rejecting a graft. If prolonged cold ischaemia is anticipated, the investigators will decline the proposed organ. The liver graft may be divided either in situ or ex situ, depending on logistical requirements and team preference. The recipient's hepatectomy will be performed in two stages, separated by no more than four months. The first stage is preferentially a left hemi hepatectomy (H234 + Spiegel lobe resection) resecting the end of middle hepatic vein, combined to a left lateral lobe transplantation and, if necessary, portal flow modulation to prevent portal hypertension. During this surgery, any potential HCC in the remnant right liver might be treated to ensure that no active nodules remain. Up to four months after the initial surgery, a right hemi hepatectomy (H5678) of the remnant native liver will be performed once satisfactory hypertrophy of the implanted left lateral lobe has been achieved. This decision will be made on a case-by-case basis after multidisciplinary assessment, taking into account potential complications,

graft recovery and the patient's condition. Graft hypertrophy and functional improvement will be monitored by multimodal assessment and the interval between the two phases will be minimized, taking into account any complications and graft function. Each patient will be followed for up to two years after the second phase of the RAPID procedure to document surgical complications and to assess the graft and the patient's overall and oncologic status. Any changes to the immunosuppression protocol compared to standard liver transplantation will be implemented as needed.

Technical consideration of liver splitting

Consistent with current practice for pediatric split liver transplantation, the surgical team will decide whether to split either in situ (prior to aortic clamping), which is the preferred method, or ex vivo at 4 °C during the back-table procedure, once the organ is received at the transplant centre. Splitting on perfusion machine will be allowed. The whole-liver will be then split into two allografts (right lobe and left lateral lobe). The grafts will be allocated by the ABM according to national distribution rules. The split will be conducted by a senior surgeon experienced in hepatic surgery. The RAPID graft is a left lateral lobe (G23), including the left hepatic vein, with possible inclusion of the scissural and the termination of the median hepatic vein (common trunk). This will facilitate a broad venous anastomosis (on both common trunks), reducing the risk of outflow block once the graft hypertrophies. The RAPID graft also includes the complete arterial axis up to the celiac trunk, the entire portal venous axis, and the left hepatic duct. An iliac arterial and venous graft from the donor will be also provided for reconstruction, if necessary. The right graft will include the right lobe with the inferior vena cava and the middle hepatic with its reconstruction. The right graft also includes the common bile duct, the right portal branch, and the right hepatic artery branch.

Surgical technique: first stage

In the first stage of surgery, left hemi-hepatectomy including resection of the Spiegel lobe (H1234) will be performed and the native left liver will be replaced with the RAPID small graft, while the native right liver will be left intact (Fig. 1).

There are several steps to this procedure. First, portal and central venous pressures, as well as portal and hepatic arterial flowmetry will be measured to establish baseline hemodynamics. Based on this information, portal modulation will be performed at the end of surgery, if

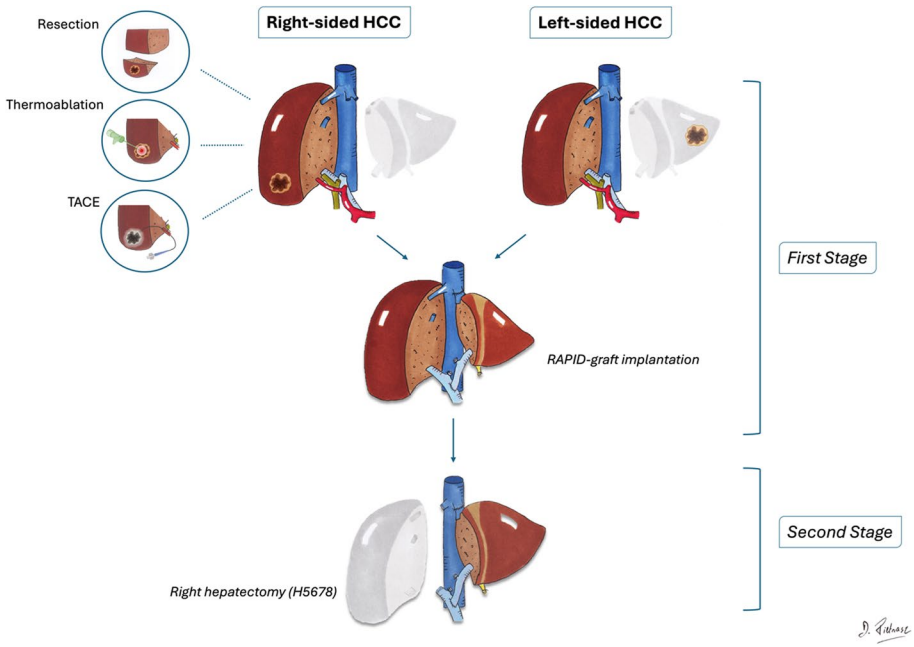

Fig. 1 Two stages of RAPID protocol. First Stage: In case of left-sided HCC, left hepatectomy (H1234) will be performed and the native left liver will be replaced with the RAPID small graft (G23), while the native right liver will be left intact. In case of right-sided HCC, the HCC must have been pre-operatively controlled by TACE or thermoablation technic. If persistent tumour activity in the right liver despite preoperative treatment, limited resection/radioablation of active HCC will be performed concomitantly with the left hepatectomy. This is followed by a left hepatectomy including resection of the Spiegel lobe (H1234) and the terminal branches of the middle hepatic vein to allow subsequent anastomosis of the common venous trunks. The native right liver will not be mobilized. Second Stage: A right hepatectomy (H5678) will be carried out using the same abdominal incision

required. In case of persistent tumour activity in the right liver despite preoperative treatment, radiofrequency or microwave ablation or limited resection of HCC will be performed. This is followed by a left hepatectomy including resection of the Spiegel lobe (H1234) and the terminal branches of the middle hepatic vein to allow subsequent anastomosis of the common venous trunks. The native right liver will not be mobilized.

The RAPID graft implantation involves:

- venous anastomosis between the common venous trunks,
- portal anastomosis between the donor portal vein and the recipient portal vein (preferably avoiding the left portal branch), ideally in a side-to-end fashion,
- arterial anastomosis between the celiac trunk of the graft to the common (or proper) hepatic artery or the stump of left hepatic artery or splenic artery of the recipient,
- biliary anastomosis with an hepaticojejunostomy between the left biliary duct and jejunum with a R-and-Y reconstruction.

At the end of the operation, portal and central pressures and flowmetry are remeasured to determine the need for portal modulation. The decision and type of modulation is at the surgeon's discretion. With strict patient selection, modulation is often avoidable. Key principles include measuring portal pressure after graft reperfusion, when the patient is flat and hemodynamically stable (Table 1).

Monitoring during interstage

In addition to the usual monitoring for all transplanted patients, which is at the discretion of each team, RAPID-HCC imposes specific rules. The maximum duration to perform the second stage is 4 months, with no fixed minimum duration; this will be decided on a case-by-case basis after approval by the surgical, anesthetic and hepatology teams. Daily graft US-Doppler is required for the first week. On day 7, an abdominal CT or MRI with contrast is performed, followed by repeat imaging every 21 days until the second stage to monitor liver volume. A minimal graft volume/body weight ratio of at least 0.8 is required. Scintigraphy with mebrofenin or another iminodiacetic acid derivative is performed every 21 days to evaluate graft function recovery and determine the functional shift to the left side, authorizing the second stage, with a desired left liver function of greater than 50% of total hepatic function. Depending on centres protocols, ICG plasma clearance might also be measured every 21 days to assess overall liver function. In rare cases, right portal embolization may be required to stimulate graft hypertrophy. The medical team will decide where the patient will recover after surgery, whether in the intensive care unit, standard ward or discharged from hospital.

Surgical technique: second stage

A right hepatectomy (H5678) will be carried out using the same abdominal incision. Before and after clamping the right pedicle elements, portal and central pressures, as well as flowmetry, will be measured to assess the need for potential portal modulation. Additionally, a surgical biopsy of the graft may be performed (Figs. 1 and 2).

Criteria for discontinuing or modifying allocated interventions {11b}

Several scenarios will be considered if any stage of the RAPID-HCC trial must be stopped prematurely:

- If the patient experiences disease progression while awaiting liver transplantation (LT) or meets any

Table 1 Algorithm for management of elevated Portal Vein Pressure (PVP) in liver transplantation

PVP—Portal Vein Pressure	*Portal Modulation intervention*
PVP ≤ 15 mmHg	No modulation required
PVP > 15 mmHg	Portal flow modulation is required until PVP is ≤ 15 mmHg
	1. Somatostatin injection IV bolus 250 µg followed by intravenous 250 µg/hour
	2. Splenic artery ligation
	3. Partial portal vein ligation (banding)
	4. Calibrated portocaval shunt
	5. Splenectomy

Flowchart illustrating the sequential interventions recommended to achieve and maintain portal vein pressure (PVP) ≤ 15 mmHg after graft reperfusion. Initial management begins with intravenous administration of somatostatin (bolus 250 µg followed by continuous infusion at 250 µg/hour). If target PVP remains unmet, subsequent steps include splenic artery ligation, partial portal vein ligation (banding), calibrated portocaval shunt, and ultimately splenectomy, progressing sequentially as needed until PVP ≤ 15 mmHg is achieved

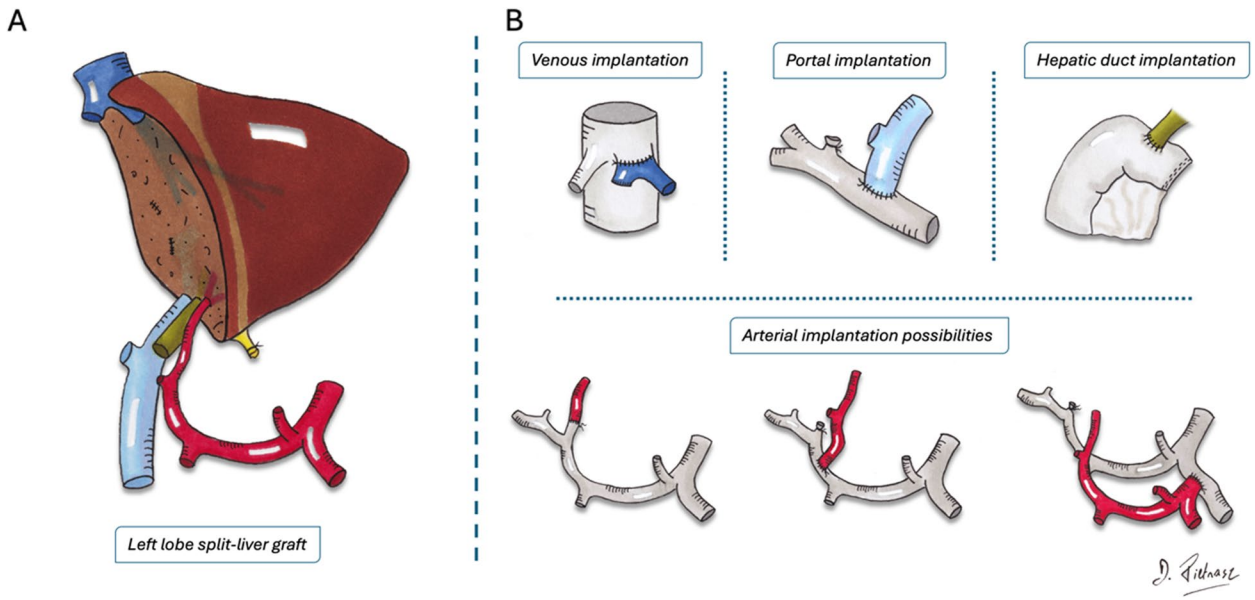

Fig. 2 Left lobe split-liver graft and graft implantation. **A** Anatomical aspect of the left lobe split-liver graft. The common portal trunk, complete arterial hepatic trunk and left hepatic duct are preserved. The suprahepatic anatomy includes the common venous trunk with left hepatic vein and the origin of the median vein. **B** The RAPID graft implantation involves (in color the graft, in grey the recipient): venous anastomosis between the common venous trunks; portal anastomosis between the donor portal vein and the recipient portal vein (preferably avoiding the left portal branch), ideally in a side-to-end fashion; arterial anastomosis between the celiac trunk of the graft to the common (or proper) hepatic artery or the stump of left hepatic artery or splenic artery of the recipient; biliary anastomosis with an hepaticojejunostomy between the left biliary duct and jejunum with a R-and-Y reconstruction

exclusion criterion (excluding age) after enrollment, the patient will be withdrawn from the study. This decision must be validated by the scientific committee. In such cases, the patient will not receive the study intervention and will exit the RAPID-HCC follow-up. Since the investigational procedure is unlikely to cause ongoing side effects or complications, these patients will transition to standard clinical care outside the protocol.

- If a patient dies while awaiting LT, the death will be recorded as a dropout in the final analysis.
- If a contraindication to LT arises during the initial RAPID phase, the patient will remain enrolled but will be classified as a "RAPID failure." Follow-up for these patients will continue for up to two years.
- If intra-abdominal or hepatic exploration during laparotomy reveals that complete resection or ablation of the right-sided tumor is not feasible, the patient will be withdrawn from the RAPID-HCC protocol, and the graft will be reassigned by the national transplant authority (ABM).

All serious adverse events (SAEs) must be documented, reported promptly to the study sponsor via email, and tracked until resolution. Documentation should be maintained both in the patient's source file and electronic case report form (eCRF). Follow-up methods will be determined by the independent monitoring committee.

Strategies to improve adherence to intervention {11c}

The study protocol does not prescribe specific strategies for improving adherence to the intervention. Instead, each investigator is encouraged to apply the adherence strategies routinely used within their institution or practice.

Relevant concomitant care permitted or prohibited during the trial {11 d}

There are no additional restrictions other than those listed in the non-inclusion criteria.

Outcomes {12}

Primary outcomes

The main objective of the RAPID-HCC trial is to evaluate the feasibility and tolerability of the RAPID procedure in patients diagnosed with hepatocellular carcinoma (HCC) who have preserved liver function.

The primary outcomes will include:

1. Successful Completion of RAPID Procedure. A successful RAPID procedure is defined as completion of both surgical stages without graft removal (explantation), patient survival, and no re-listing for transplantation at four months following the second surgical step. Conversely, RAPID is considered unsuccessful if graft explantation, patient death, or re-listing for transplantation occurs within four months after the second surgical stage.
2. Tolerability of the RAPID Procedure. Tolerability will be assessed based on adverse events specifically linked to the procedure, beginning from the first surgical intervention up to 90 days after the second surgical stage. Morbidity after each surgical stage will be evaluated using the standardized Clavien Classification (CCI score) [32]:

   After the first stage: Morbidity will be assessed at the end of the auxiliary LT and until the second stage if it occurs. If the second stage does not occur, morbidity will be evaluated until day 90 (if the hospitalization duration is less than 90 days) or until the end of hospitalization (if the hospitalization duration exceeds 90 days).
   After the second stage: Morbidity will be assessed from the end of the second stage until day 90 (if the hospitalization duration is less than 90 days) or until the end of hospitalization (if the hospitalization duration exceeds 90 days).

Secondary outcomes

Secondary outcomes include the analysis of the graft survival at 4 months from the first surgical stage and at 2 years post-transplantation and the patient survival at 2 years from listing and at 2 years post-transplantation.

The survival of RAPID grafts at 4 months from the first surgical stage will be defined as a RAPID graft still in place, regardless of whether the second surgical stage has been performed, with non-survival defined as graft explantation, patient re-listing, or patient death within 4 months of the first stage. Graft survival at 2 years post-transplantation will be considered if the graft is still in place; non-survival will be defined by patient death or re-transplantation. The study will record the number of patients who died from any cause within 2 years post-listing and within 2 years post-transplantation (first stage of RAPID). Histologically proven rejections within 2 years post-RAPID (post first stage) will be documented, excluding rejections on a second graft in case of re-transplantation. The incidence, location, and timing of HCC recurrences within 2 years post-first stage of RAPID will be documented by typical imaging (CT or MRI), AFP elevation, or histological evidence. The time between listing on the waiting list and transplantation according to RAPID (first stage) will be monitored in months. The total number of additional grafts obtained according to the RAPID protocol will be calculated as the number of left lobes transplanted according to the RAPID protocol minus the number of re-transplantations, providing a net organ gain. The number of right livers generated and transplanted, as well as complete RAPID procedures (excision of native liver) will be analyzed. The dropout rate (exclusion from the transplantation programme) in the RAPID group will be estimated and compared to the control group. Finally, the waiting time between listing and transplantation in the RAPID group will be compared to the control group.

Participant timeline {13}

The trial time-line will include:

Selection visit

The selection visit occurs between 8 days and 6 months before study enrollment. During this visit, participants receive comprehensive study information. After an adequate period for reflection, informed consent must be obtained. Patients may sign consent the same day or after a 7-day reflection period, but consent must precede the pre-transplant evaluation. Enrollment in the trial is only finalized after validation by the Scientific Committee.

A pre-transplant evaluation typically requires up to 3 months. If uncertainties arise, additional tests may extend this by up to 3 additional months. Inclusion is officially completed following standard and study-specific assessments. After this, exemption points will be requested from the Agence de Biomédecine (ABM), which requires the RAPID-HCC registration number.

The standard assessment tests required by RAPID-HCC as part of the pre-inclusion assessment will be:

- Volumetry of the native liver (total liver, right liver, left liver) from a recent abdominal CT scan, or MRI,
- Verification of the completion of double PET/CT (choline + FDG), or MRI, routinely performed by the 5 participating centers for all HCC patients being considered for liver transplantation (within the last 3 months),
- Blood tests, including serology (HIV, hepatitis B, hepatitis C) and AFP level.

The specific tests required by RAPID-HCC as part of the pre-inclusion assessment will be:

- Optional: pre-transplant plasma clearance of indocyanine green (ICG) for subsequent follow-up after the first stage of RAPID transplantation to assess graft function recovery. This involves a blood test with three repeated samples every five minutes (approximately 5 ml each) to monitor the decline in plasma concentration of the dye eliminated by the liver.
- Measurement of supra-hepatic pressures (free and wedged) via transjugular access under local anesthesia, either during hospitalization for pre-transplant assessment or during specific outpatient hospitalization. This measures the portocaval gradient, estimates the degree of portal hypertension, and evaluates the possibilities for auxiliary grafting. Some centers already carry out this examination as part of their routine pre-HT assessment.

Inclusion visit

Inclusion and exclusion criteria are verified by reviewing results from both standard and protocol-specific evaluations. Interpretation of imaging, ascites history, volumetry, and ICG clearance tests is left to the discretion of each clinical team and the Scientific Committee. However, a pre-transplant portocaval gradient must be below 20 mmHg (normal $\leq$5 mmHg). Gradients above this threshold represent excessive risk for postoperative small-for-size syndrome, based on prior evidence showing increased risks with gradients $\geq$15 mmHg after transplantation.

Follow-up visits for the study after inclusion and before the first surgical stage of RAPID

These follow-up visits will occur according to the usual schedule (internal policy) of each team. No specific examination is required. In case of an intercurrent event (appearance of ascites, new HCC nodule(s), portal thrombosis, etc.), the case must be presented to the scientific committee (refer to "premature termination visit" below). Compliance with inclusion and exclusion criteria will be re-verified before the first surgical stage using clinical care data only.

First stage of RAPID

Partial hepatectomy and auxiliary graft of the left lateral lobe.

Interval between the two surgical stages

Patients will be hospitalized or discharged based on their clinical evolution. They will be re-evaluated to authorize the second stage once the graft has a volume and function compatible with maintaining satisfactory hepatocellular functions post-hepatectomy. Follow-up includes: ICG plasma clearance approximately every 21 days, mebrofenin, or any other iminodiacetic acid derivative, scintigraphy approximately every 21 days, injected abdominal CT-scan, or MRI, on day 7 and approximately every 21 days (minimum threshold: ratio >0.8 between graft volume and body weight) and volumetry calculation, daily Doppler ultrasound for the first 7 days post-operation, no change in standard biological follow-up (complete blood count [CBC], ionogram, liver tests, etc.) and the AFP measurement on day 21. Verification of the absence of post-operative medical-surgical complications and eligibility for the second-stage hepatectomy will be assessed by clinical and biological examination left to the discretion of the surgical and anesthetic team. Complications recorded according to CCI score until day 90 or until the end of hospitalization (if duration >90 days).

Second stage of RAPID

Resection of the right liver or right lobe.

Follow-up visits after the second stage of RAPID

The post-transplant follow-up protocol includes several steps to monitor the patient's recovery and the functional health of the left liver graft. On days 8 and 30 after transplantation, CT scans, or MRI, are performed to assess liver volume and blood flow, and regular Doppler ultrasound is performed according to local guidelines. Standard biological tests and immunosuppression protocols, including CBC, ionogram and liver function tests, will remain the same for patients not included in the protocol. Follow-up appointments with the surgeon or hepatologist will be scheduled 30 days after the second procedure and then at 3, 6, 9, 12, 15, 18, 21 and 24 months, with alpha-fetoprotein (AFP) measurements at each visit. Enhanced CT scans and liver MRI will be performed at 3, 9, 18, 6, 12 and 24 months and Doppler ultrasound at 15 and 21 months. There is no fixed length of hospital stay between the two phases of the protocol or after the second phase; this will be adjusted according to the patient's progress and any complications. Depending on how well the patient is recovering after surgery, they may be discharged home or to a recovery facility before the second stage, or they may have the second stage during the same hospital stay. The timing of the second stage is not predetermined, but is based on various tests, including plasma clearance, scintigraphy, volumetry and biological assessments. These assessments will help to confirm that the liver transplant is functioning well and will guide the overall decision-making process for the second operation (Fig. 3).

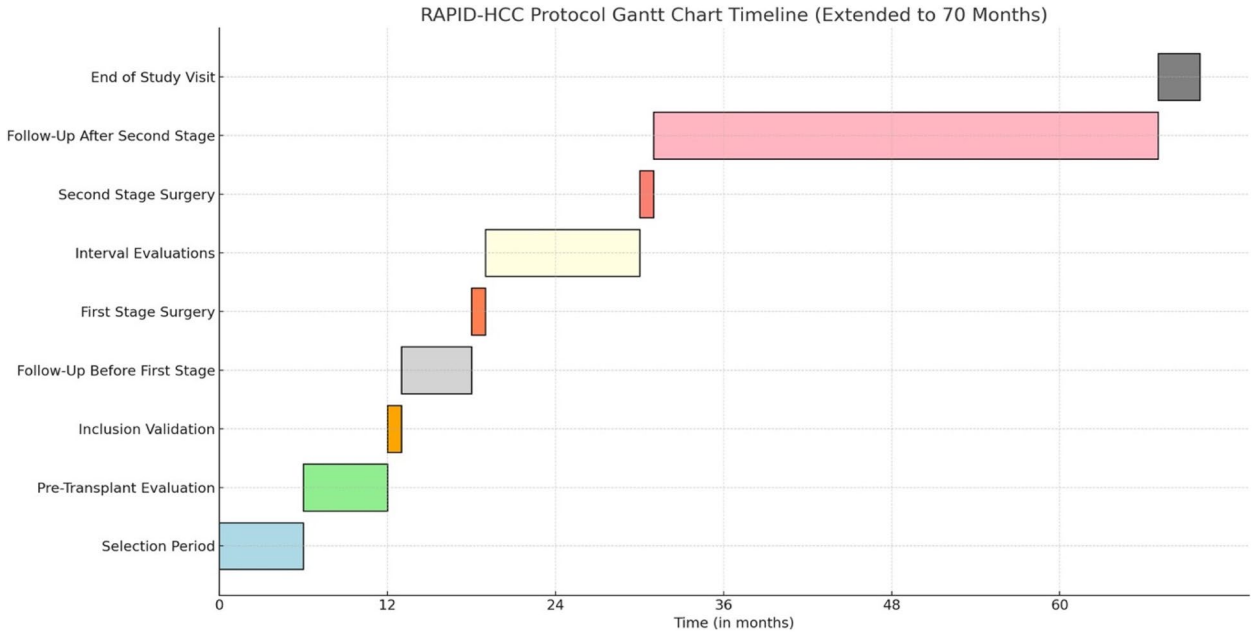

Fig. 3 RAPID-HCC trial timeline chart. The RAPID-HCC Protocol includes the following phases: Selection (0–6 months, informed consent); Pre-Transplant Evaluation (6–12 months, imaging and serology); Inclusion Validation (12–13 months, committee approval); Pre-Surgical Follow-Up (13–18 months, routine checks); First Surgery (18–19 months, partial hepatectomy with auxiliary graft); Interval Evaluations (19–30 months, graft monitoring via imaging and ICG tests); Second Surgery (30–31 months, right liver resection); Postoperative Follow-Up (31–67 months, routine imaging and labs); End-of-Study Visit (67–70 months, final AFP measurement and imaging)

End of study visit

The study visit will end 2 years after the second phase of the RAPID procedure. Apart from AFP measurement and MRI conducted as part of routine care, as previously mentioned, no other systematic examinations will be performed. Subsequent follow-up will be at the discretion of the treating team according to local policy.

Premature termination visit

Before the first surgical stage, patients may be withdrawn if new exclusion criteria arise (excluding age-related criteria). The Scientific Committee (SC) reviews such cases during routine preoperative surveillance. SC determines whether the patient continues in the RAPID-HCC trial. If removed, the patient's care will proceed according the standard guidelines.

Premature termination visit

Before the surgical stage, patients may be withdrawn if new exclusion criteria arise (excluding age-related criteria). The Scientific Committee reviews such cases during routine preoperative surveillance. The committee determines whether the patient continues in the RAPID-HCC protocol or is removed entirely, including from the ABM transplant waiting list. If removed, the patient's care will proceed according to standard guidelines.

Sample size {14}

We plan to transplant 34 patients in this pilot study. To achieve the transplantation of 34 patients, and taking into account potential drop-outs, contraindications to liver transplantation in the first phase, whole liver transplantation prior to the RAPID procedure, or matching/logistical difficulties between recipient and donor, we propose to enroll a total of 50 patients. This larger number of selected recipients will give the surgeons a better chance of achieving a perfect graft-recipient match and optimizing the procedure. We expect to enroll less than one patient per center per month.

Recruitment {15}

Information about the study and opportunities for patient enrollment will be shared at national and international conferences attended by oncologists, hepatologists, and liver surgeons. Healthcare professionals will receive clear explanations of the study objectives, inclusion and exclusion criteria, and overall protocol. Brochures and flyers will also be distributed. To enhance visibility and recruitment, the trial will be listed on clinical trial registries and online platforms, with regular updates shared through social media and professional networks.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Study follow-up visits will take place at each center initially every month and then every three months for the first three years, followed by every six months thereafter. Mandatory follow-up tests will include MRI or CT scans or US of the liver, blood tests including tumor markers.

Plans to promote participant retention and complete follow-up {18b}

All subjects in the study will be followed up for the duration of the study. Patients who discontinue follow-up without withdrawing consent will still be monitored for survival. The patient follow-up pathway will follow standard clinical practice, with patients being seen regularly and complying with scheduled follow-up visits. Data return is facilitated by regular communication between the trial team and the recruitment sites. As patient follow-up is conducted through review of medical records, no additional specific plans are required.

Data management {19}

Patient data will be collected electronically using the eCRF Cleanweb, a secure online platform set up by the data manager. Data entry begins as soon as informed consent is obtained. Designated site staff will input required information, while the principal investigator at each site ensures accuracy and completeness. Investigators will review and sign off on each entry. Any missing assessments will be documented, and corrections will be tracked. All data will be finalized before database closure.

Statistical methods

Statistical methods for primary and secondary outcomes.

Statistical methods for primary and secondary outcomes {20a}

Descriptive analyses

Qualitative variables will be described using numbers and percentages, while quantitative variables will be presented as the mean ± standard deviation or the median (min–max), based on their distribution.

Statistical analysis to test feasibility of the RAPID Procedure (Primary Evaluation Criteria)

Sequential boundaries will be employed to monitor the failure rate of the RAPID procedure, generating a Pocock-type boundary. The trial assumes a maximum planned sample size of 34 patients, with a 0.3 probability of feasibility failure and a 0.05 probability of early termination. The trial will be terminated if the number of RAPID failures reaches or exceeds the theoretical threshold, defined as the number of feasibility failures in the enrolled patients. This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.3, using a one-sided test with an alpha of 0.014750. This boundary will be employed to monitor the feasibility rate of the RAPID procedure. Enrollment will be halted if an excessive number of failures is observed, that is, if the number of failures is equal to or exceeds b_n out of n patients enrolled. Moreover, whenever the number of feasibility successes is strictly less than $(n - b_n)$, a 4-month follow-up period after the latest time point (Time 2) of the most recently enrolled patient will be observed (pause in enrolments) to ensure that we do not reach the boundary b_n which would indicate the trial's termination.

Statistical analysis to test the tolerance of the RAPID procedure

Adverse events (AEs) related to each stage of the treatment will be described according to their nature and severity. Data collection will include early events, medium-term events (3 months), and long-term events (12 months and 24 months). The Comprehensive Complication Index (CCI) score will be calculated.

Secondary evaluation criteria

Since the power calculation was performed for the analysis of the primary objective, the results of the secondary analyses will be exploratory. A post-hoc power calculation may be conducted.

A McNemar test will be used to compare the delisting rate between patients who underwent the RAPID procedure and those who underwent the standard procedure.

The overall survival of patients at 2 years from listing in each group (RAPID procedure versus standard procedure) will be compared using conditional logistic regression. The same method will be employed for the analysis of overall survival at 2 years from listing and the analysis of graft survival at 2 years post-transplant.

Analyses of the morbidity associated with the RAPID procedure after the first and second stages of the surgical protocol, the incidence of histologically confirmed rejection after RAPID, the incidence and location of HCC recurrence at 2 years post-transplant according to the RAPID procedure, the time from listing to transplant according to the RAPID procedure, and the actual gain in grafts obtained through the RAPID procedure will be descriptive.

Statistical significance

The analysis of the primary objective will be conducted using a one-sided test with an overall alpha risk of 5%. The analysis of the secondary objectives will be conducted using two-sided tests with an alpha risk of 5%.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

All efforts will be made to avoid missing data. The methods for addressing missing data will be detailed in the statistical analysis plan.

Oversight and monitoring

Composition of the coordinating center and trial steering committee.

Composition of the coordinating centre and trial steering committee {5d}

The Trial Coordination Center (TCC) is composed by a multidisciplinary team of experts, including principal investigators, project managers, data analysts and administrative support staff. This team is responsible for overseeing the day-to-day trials' development, ensuring compliance with the protocol, managing data collection, and maintaining communication with all participating sites. The Trial Steering Committee (TSC) consists of independent experts in the field, sponsor representatives and key opinion leaders. The primary role of the TSC is to provide oversight to ensure that the trial is conducted to the highest scientific and ethical standards. They meet regularly to review progress, address any issues that arise and make decisions about trial amendments or interim analyses as required. A Scientific Committee (SC) has been also established to endorse specific tasks, including validating the selection criteria and pre-inclusion outcomes for patients proposed for inclusion. SC is also responsible for approving continued enrolment or deciding on early termination if a significant event occurs prior to transplantation, such as portal vein thrombosis or tumour progression.

Composition of the data monitoring committee, its role and reporting and reporting structure {21a}

The sponsor is responsible for ensuring the safety and respect of people participating in research and for establishing a quality assurance system to monitor progresses of the trial. To achieve compliance, the sponsor appoints Clinical Research Associates (CRAs) to make regular follow-up visits to the trial sites. For this high-risk research, the choice of an appropriate level of monitoring was weighted according to the complexity, impact, and budget of the research. Accordingly, the sponsor, in agreement with the TCC, determined the logistical and impact score to establish the level of monitoring required: maximum level. A CRA (agreed by the sponsor) will oversee the proper conduct of the research, ensuring the collection, documentation, recording, and reporting of data in accordance with the Standard Operating Procedures (SOPs) within the DRCI and in compliance with Good Clinical Practice and applicable legal and regulatory requirements. The investigator and their team agree to be available for regular quality control visits by the CRA, during which elements such as written consent, adherence to the research protocol and defined procedures, the quality of data collected in the case report form and the management of used products will be reviewed according to the monitoring level.

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct {22}

Serious adverse events (SAE) will be reported for both treatment arms according to the GCP guidelines. A serious adverse event is defined as one that results in death, that is life-threatening to the research participant, that necessitates hospitalization or prolongation of existing hospitalization, that leads to significant or prolonged disability or incapacity, or that results in a congenital anomaly or malformation.

Other events requiring immediate notification by the investigator to the sponsor include:

1. Events related to partial hepatectomy (stage 1): liver failure.
2. Events related to transplantation of a partial graft in the context of portal hypertension (stage 1): small-for-size syndrome (clinical, biological, or radiological manifestations such as ascites, jaundice), portal vein thrombosis.
3. Events related to the implantation of a partial graft: stenosis or thrombosis of the portal, supra-hepatic, or arterial vessels.
4. Second surgical stage: digestive complications during the second stage in case of difficult adhesiolysis.

The investigator assesses the severity of each adverse event and must notify the sponsor of all SAEs and serious incidents during the trial within 24 h, except for those exempted by the protocol. The initial notification requires a written report, followed by detailed written reports within 8 days. The investigator must thoroughly document the event with anonymized copies of relevant laboratory results or reports, provide a medical diagnosis,

and establish a causal link between the SAE, the medical device, and the procedure. The patient must be followed until the event is fully resolved, stabilized to an acceptable level, or returned to their previous state, regardless of trial withdrawal.

Frequency and plans for auditing trial conduct {23}

The sponsor and competent authorities will conduct quality assurance audits and inspections. All data, documents, and reports are open to audit and regulatory inspection without invoking medical confidentiality. These audits may be conducted at any time by individuals appointed by the sponsor, independent of the research leaders, to ensure the research's quality, the validity of its results, and compliance with legal and regulatory standards. Research leaders and supervisors are committed to meeting the sponsor's and authorities' requirements during audits or inspections, which may cover all stages of the research, from protocol development to the publication of results and data archiving. Investigators agree to accept quality assurance audits by the sponsor and inspections by regulatory authorities, allowing access to all data without invoking medical confidentiality. Routine monitoring, detailed in the trial monitoring plan, involves moderate intensity with one visit or call per year. Most data are monitored centrally to maintain trial integrity, ensure patient safety, and oversee primary endpoints. Thus, annual monitoring will be conducted via telephone or video conferencing, with bimonthly central monitoring of key data points. This approach upholds compliance and scientific integrity throughout the study.

Plan for communicating important amendments to relevant parties {25}

Any changes to the protocol that might affect the conduct of the trial, the potential benefit to patients, or patient safety, including changes to the trial objectives, design, patient population, sample sizes, procedures, or important administrative aspects, will require a formal amendment. These amendments must be agreed by both the principal investigator and the sponsor, documented in a new version of the protocol signed by both parties, and approved by the Scientific Committee (SC) and Ethics Committee prior to implementation in accordance with local regulations. The sponsor is responsible for obtaining the necessary Ethics Committee and regulatory authority approvals and for communicating these amendments to the participating sites. Any substantial amendments to the protocol or other essential documents will be notified to the relevant regulatory authorities and the Ethics Committee. Implementation of any substantive amendment may proceed only after formal approval by the Ethics Committee and the regulatory authority.

Who will take informed consent? {26a}

Eligible patients will be invited to participate to the study. The investigators will obtain informed consent from each subject in accordance with ethical standards. Adequate time will be allowed for reflection between the provision of information and the consent form signing. Each participant must provide informed consent, which must be freely given and documented by a signed consent form from both the participant and an investigator before any study-specific procedures. After validation by the scientific committee, enrolment will be confirmed. The consent form will explicitly ask participants to agree to the use of their data. Participants will also be asked to consent to the sharing of relevant data with staff at participating universities or regulatory authorities, as appropriate. Accordingly, any additional testing will only take place after informed consent has been obtained, ensuring that each participant's participation and consent to these procedures is entirely voluntary.

Additional consent provisions for the collection and use of participant data and biological specimens {26b}

No additional studies that may use the data collected in this trial are planned.

Confidentiality {27}

Article L.1121–3 of the Public Health Code guarantees that all information relating to this study is kept confidential, in particular the identity of the participants and their results. All data from trial participants will be anonymized to protect their identity. Individuals' names and addresses will not be recorded or disclosed. Instead, only the initials of their first and last name and a coded number will be documented. This ensures that all data remain confidential and that participants' identities are protected throughout the trial. The sponsor will verify that each participant has given written consent for their data to be used for quality control purposes only.

Dissemination plans {31a}

In accordance with local regulations, progress reports and a final report will be prepared by the sponsor and submitted to the reviewing ethics committees. The publication policy outlined in the agreements between the participating centers will ensure that results are presented at scientific congresses and published in peer-reviewed journals. These results will also be incorporated into clinical practice guidelines for the gastroenterology and hepatology community. Upon completion of the study, the data will be analyzed and a final report will be prepared. Participants involved in key aspects of the trial will be listed as authors and publications will follow international reporting guidelines.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The data supporting the findings of this study are available from the corresponding author, [NG], upon reasonable request. Access to the internal repository data for other researchers will require approval from an ethics commission. The Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), and Clinical Study Report will be publicly shared. However, participant-level datasets will only be accessible following ethics commission approval.

Plans for collection, laboratory evaluation, and storage of biological specimen for genetic or molecular analysis in this trial/future use {33}

In this trial, the collection, laboratory evaluation, and storage of biological specimens for future genetic or molecular analysis are not anticipated. Consequently, no provisions or protocols have been established.

Discussion

The RAPID-HCC trial introduces a novel surgical approach to liver transplantation (LT) aimed at improving organ availability and patient survival. Early studies suggest that the RAPID procedure optimizes donor organ use by enabling the division of a deceased donor liver, allowing two adult recipients to benefit from a single graft. This technique has the potential to significantly increase the number of transplants performed, thereby reducing waiting times and transplant-related mortality. A key advantage of the RAPID procedure is its two-stage hepatectomy, which enhances both safety and functionality. By preserving the native right liver during the initial post-transplant period, patients retain sufficient liver function, potentially lowering the risk of early postoperative complications. The second stage, involving the removal of the native right liver once the transplanted left lobe is fully functional, ensures a smooth transition to complete graft dependence, which may improve long-term outcomes. The trial's structured assessment of primary and secondary outcomes provides a comprehensive evaluation of the procedure's feasibility, safety, and efficacy in patients with hepatocellular carcinoma (HCC). Primary outcomes focus on procedural success and adverse event monitoring, while secondary outcomes include graft survival, patient survival, incidence of graft rejection, HCC recurrence, and overall patient quality of life. This rigorous evaluation will generate robust data to validate or challenge preliminary findings. However, the widespread implementation of the RAPID procedure presents certain challenges. The complexity of the two-stage surgical approach demands significant expertise and institutional resources, which may limit immediate adoption in all centres. Additionally, long-term studies are required to assess graft durability and its impact on patient quality of life over time. Given the high prevalence of HCC and the ongoing shortage of donor livers, the RAPID procedure could provide a viable solution for many patients who would otherwise face prolonged waiting times and an increased risk of mortality. This trial will offer crucial insights into the procedure's clinical value and feasibility, potentially establishing a new benchmark in liver transplantation. If successful, the RAPID procedure could mark a major breakthrough, increasing organ availability and improving outcomes for patients with HCC.

Trial status

The current trial protocol is version V4.0 dated 11 June 2024. The trial opened to recruitment on July 2024. Recruitment is anticipated to run for 24 months, and therefore, the estimated completion date is May 2029.

List of study sites

Paul Brousse Hospital, Villejuif, Assistance Publique Hôpitaux de Paris;

Pitié Salpêtrière Hospital, Paris, Assistance Publique Hôpitaux de Paris;

Beaujon Hospital, Clichy, Assistance Publique Hôpitaux de Paris;

Pontchaillou Hospital, CHU de Rennes;

University Hospital of Lyon, CHU de la Croix Rousse.

Abbreviations

ABM	Agence de la Biomédecine (Agency of Biomedicine)
ACLF	Acute-on-Chronic Liver Failure
AFP	Alpha-Fetoprotein
CCI	Comprehensive Complication Index
HCC	Hepatocellular Carcinoma
CHU	Centre Hospitalier Universitaire (University Hospital Centre)
DDLT	Deceased Donor Liver Transplantation (Liver Transplantation from a Brain-Dead Donor)
e-CRF	Electronic Case Report Form
FDG	Fluorodeoxyglucose
ICG	Indocyanine Green
MRI	Magnetic Resonance Imaging
LDLT	Living Donor Liver Transplantation
MELD	Model for End-Stage Liver Disease
NFS	Numération Formule Sanguine (Complete Blood Count, CBC)
RAPID	Resection And Partial Liver Transplantation with Delayed Hepatectomy (Auxiliary Partial Liver Transplantation with Native Liver Hepatectomy in Two Successive Operations)
CT	(Computed Tomography, CT)
LT	Liver Transplantation
TIPS	Transjugular Intrahepatic Portosystemic Shunt
TKI	Tyrosine Kinase Inhibitor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14127-7.

Supplementary Material 1.

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Financial and other competing interests {28}
The authors declare that they have no competing interests. None of the authors have any financial, personal or professional conflicts that could be perceived as influencing the results or interpretation of this study. All authors contributed to the research and preparation of the manuscript without bias or external pressure

Authors' contributions
A.P. wrote the manuscript. D.P. conducted investigations, curated data, and prepared figures. E.D. and L.C. developed the methodology, curated data and performed formal analysis. O.S., C.G., J.-Y.M., K.M., M.L., S.D., H.J., K.B. conducted investigations and provided resources. M.-A.A., R.A., A.S.C., D.A., D.C., E.V. conducted investigations, provided resources and contributed to methodology. N.G. conceptualized the study, developed the methodology, prepared the original draft, acquired funding, supervised the study and administered the project. N.G. also reviewed and edited the manuscript. All authors reviewed the manuscript.

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Data availability {29}
The final dataset will be managed by R or Sas Software. The chief investigators will have access and can authorize exceptional access for other trial team members to support analysis or during absences. Additional analyses of the dataset will be allowed with the agreement of the trial review committee, in accordance with the trial publication policy.

Declarations

Ethics approval and consent to participate {24}
The RAPID-HCC trial has received ethical approval from the National Ethics Committees in France: ANSM – Agence de sécurité du médicament et des produits de santé et Comité de protection des personnes Ile de France III (Ethics approval number 2022-A02151 - 42). All participating centers involved in this multi-centre study, have obtained local ethical approvals as required by French regulations. Informed consent will be obtained from all participants prior to their enrollment in the trial. The consent process will include a comprehensive explanation of the study's purpose, procedures, potential risks, and benefits. Participants will be given opportunity to ask questions and will be informed of their right to withdraw from the study at any time without any consequence to their ongoing medical care This study adheres to the principles outlined in the Declaration of Helsinki and complies with the ethical standards of the institutional and national research committees. The confidentiality and anonymity of all participants will be strictly maintained throughout the study.

Consent for publication {32}
Not applicable—this document does not contain any identifying images or personal or clinical details of participants, nor will such details be included in any future study reports. For access to participant information materials and the informed consent form, please contact the corresponding author.

Competing interests
The authors declare no competing interests.

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