Dragon 1 Protocol Manuscript: Training, Accreditation, Evaluation and Safety Evaluation of Portal and Hepatic Vein Embolization (PVE/HVE) to Accelerate Future Liver Remnant (FLR) Hypertrophy

R. Korenblik, R.M. van Dam

Methods

Embolication of the FLR in patients with borderline resectable colorectal cancer liver metastases.

Abstract

Study Purpose: The DRAGON 1 trial aims to assess training, implementation, safety and feasibility of combined portal- and hepatic-vein embolization (PVE/HVE) to accelerate future liver remnant (FLR) hypertrophy in patients with borderline resectable colorectal cancer liver metastases.

Methods: The DRAGON 1 trial is a worldwide multicenter prospective single arm trial. The primary endpoint is a composite of the safety of PVE/HVE, 90-day mortality, and one year accrual monitoring of each participating center. Secondary endpoints include: feasibility of resection, the used PVE and HVE techniques, FLR-hypertrophy, liver function (subset of centers), overall survival, and disease-free survival. All complications after the PVE/HVE procedure are documented. Liver volumes will be measured at week 1 and if applicable at week 3 and 6 after PVE/HVE and follow-up visits will be held at 1, 3, 6, and 12 months after the resection.

Results: Not applicable.

Conclusion: DRAGON 1 is a prospective trial to assess the safety and feasibility of PVE/HVE. Participating study centers will be trained, and procedures standardized using Work Instructions (WI) to prepare for the DRAGON 2 randomized controlled trial. Outcomes should reveal the accrual potential of centers, safety profile of combined
PVE/HVE and the effect of FLR-hypertrophy induction by PVE/HVE in patients with CRLM and a small FLR. Trial Registration Clinicaltrials.gov: NCT04272931 (February 17, 2020). Toestingonline.nl: NL71535.068.19 (September 20, 2019).

Keywords Colorectal cancer liver metastases (CRLM) · Portal vein embolization (PVE) · Hepatic vein embolization (HVE) · Combined portal- and hepatic vein embolization (PVE/HVE) · Liver hypertrophy · Future liver remnant (FLR)

Introduction

Background and Rationale

Removal of colorectal liver metastases (CRLM) has been shown to improve survival of patients with stage IV colorectal cancer. However, many patients with multifocal liver metastases require resections that might put them at risk of post-hepatectomy liver failure (PHLF) [1]. When resection of more than 70% of functional liver volume in normal functioning livers or more than 60% in damaged livers is necessary, patients are at high risk of developing PHLF, which increases the risk of perioperative mortality [2]. These patients are therefore often considered primarily unresectable or potentially resectable (PU/PR), based on computed tomography volumetry of the future liver remnant (FLR) [3]. The most commonly applied method to avoid PHLF is to induce hypertrophy of the FLR before surgery, usually by portal vein embolization (PVE) [4].

PVE involves the embolization of the portal venous system to one side of the liver, inducing growth of the other side (FLR). After PVE, an FLR increase up to 40% can be observed after 3–6 weeks [5]. However, several studies showed that only 60–70% of patients underwent hepatectomy after PVE [6–10], due to insufficient hypertrophy or disease progression. Interest has consequently focused on the question whether rapid hypertrophy can be induced without a two-stage hepatectomy such as Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS, supplementary paragraph 1) [11–15].

Right hepatic vein embolization following PVE was first described in a case report in 2002 by Nagino et al. showing the applicability of the technique [16]. Consequently, small cohort studies were performed to investigate this combined procedure [17]. Experiments in pigs showed that an abrogation of hepatic vein outflow from the deportalized side accelerates regeneration similar to ALPPS [18]. All of these findings led to the development of a novel clinical approach to induce liver growth by combined Portal and Hepatic Vein Embolization (PVE/HVE). Guiu et al. performed the first variation adding glue to the PVE/HVE procedure, Liver Venous Deprivation (LVD), in humans [19]. They showed that FLR increased from 28.2% (range 22.4–33.3%) to 40% (33.6–59.3%) 23 days after this procedure with the largest increase in the first 7 days [19, 20].

To assess the clinical value of PVE/HVE in patients eligible for extended liver resection and small future liver remnants, and to safely implement a new technique, the worldwide DRAGON collaborative was initiated in 2017.

Methods

Objectives

The primary objective of DRAGON 1 is to assess the safety of the PVE/HVE procedure together with obtaining insight in the accrual ability of each individual center. Structured training in the novel technique should increase safety and allow for initial experience for those centers unfamiliar with the procedure in the DRAGON 1 trial.

Secondary objectives of DRAGON 1 are to assess the efficacy of PVE/HVE and the different PVE/HVE techniques. The latter to optimize the procedure prior to the DRAGON 2 trial.

Study Setting/Design

The DRAGON 1 trial is an International Multicenter trial for safety and feasibility evaluation of PVE/HVE. Most of the participating centers are Academic Hospitals. For a detailed list of the participating countries and their study sites see supplementary table 1.

In the DRAGON 1 trial, PVE/HVE will only be performed in patients with primarily unresectable/ potentially resectable (PU/PR) Colorectal Cancer Liver Metastases (CRLM). The total study duration for a center in the DRAGON trial 1 will be 24 months, with 12 months inclusion and 12 months follow-up. For each center, the inclusion phase will last a year after the first enrollment. The follow-up phase will last a year after the second stage resection of the last patient. Patients who do not proceed to surgical resection after PVE/HVE will also be routinely assessed until one year after combined PVE/HVE.

Eligibility

All participating centers must obtain local ethical review board approval, and if needed according to local regulations, radiation protection approval. Centers can apply for
enrollment if, based on center volume, the minimum number of inclusions of three patients within one year can be achieved. International participants’ Insurance is provided by the sponsor. Patients diagnosed with PU/PR colorectal liver metastases will be recruited via referral from the oncology, surgery, IR clinics, and local tumor boards of the participating centers. The inclusion and exclusion criteria are displayed in Table 1.

### Intervention

In combined PVE/HVE, the portal vein branch of one side of the liver and hepatic vein(s) draining the same side will be occluded to induce hypertrophy on the contralateral side [21]. PVE is performed according to local standard practice, with technical modifications between centers being allowed, to assess optimal approach for the DRAGON 2 trial. The PVE-technique used will be registered. Once access to the target portal vein has been obtained, the vein will be occluded using either a mixture of Lipiodol/cyanoacrylate, particles and coils or other embolization materials, according to local practice. After the procedure, the access sheath is retracted and the track occluded. Subsequently, HVE is performed in the same session or within 48 h using either a trans-jugular approach, a trans-hepatic approach or a transfemoral approach, according to the preference of the interventionist. Through a sheath, appropriately sized Amplatzer Vascular Plug(s) (type I,II, or IV) are introduced into the draining (usually right and sometimes middle) hepatic vein branches of the affected liver side. The number of hepatic veins to be occluded is left to the local team and depends on the individual anatomy of the liver. At least one large draining vein must be occluded.

All procedures were defined in centrally designed Work Instructions (WI) improving adherence to the interventions and subsequent study tasks.

### Participant Timeline

After recruitment \((t = 0)\), patient information and demographics are recorded. It is anticipated that a number of the included patients require a two-stage approach. The first step is to clean the FLR. A few days after, preferably in the same hospitalization, PVE/HVE is performed. One week after PVE/HVE, the first volumetry CT-scan is performed. If the FLR-volume is still insufficient, volumetry will be repeated at week three and week six. Once the FLR has reached a sufficient volume, resection is scheduled. After liver resection and the postoperative hospital stay, follow-up visits are scheduled at one, three, six, and twelve months. All diagnostic tests/ treatment procedures and visits are in accordance to standard clinical practice, except for the hepatic vein embolization during the intervention. All study visits are listed in the DRAGON 1 Flowchart (Fig. 1) and all study measures can be found in the SPIRIT Chart (Supplementary table 2).

### Primary Outcome

The primary outcome is a composite of two endpoints. Namely, the 90-day morbidity and mortality after PVE/HVE and the accrual of each participating center. Morbidity is assessed according to the Dindo-Clavien classification [22]. Accrual is defined as the time for each participating center from Site Initiation Visit (SIV) until 3 safe inclusions.
Secondary Outcomes

Secondary endpoints comprise short- and long-term surgical and oncological outcomes. These include used neoadjuvant systemic treatment, PVE/HVE intra procedural data, FLR-hypertrophy, time to adequate FLR, resection rate, time to resection, intra operative data, number of oncological procedures performed besides PVE/HVE, recurrence, 1-year disease-free and overall survival.

Sample Size

Prior to initiation, each participating center confirmed that a minimum of 3 inclusions within one year should be feasible. We expect that approximately 40 centers will be initiated in the DRAGON 1 trial. Therefore, the intended number of patients evaluated in the DRAGON 1 multicenter trial is $n = 120$ (40 centers times 3 patients per center). If the target of $n = 120$ is not reached, the trial will be evaluated regardless.

Data Collection and Management

Pseudonymized data (coded by a study ID) will be entered in CASTOR secure online trials systems (Castor BV, Amsterdam, The Netherlands) and maintained by the Clinical Trials Center Maastricht. For further details see supplementary paragraph 4.

Data protection in the DRAGON 1 trial will be in compliance with the General Data Protection Regulation (EU).

Statistical Analysis

For DRAGON 1, we will use descriptive coefficients to summarize outcomes. IBM SPSS Statistics will be used to display the results. A central interim analysis will be performed after enrollment of every 20 participants.

Access to the datasets used and analyzed during the study are available in a fully anonymized form from the sponsor upon reasonable request.

Monitoring

Site Initiation Visit (SIV), Interim Visit, and Close Out Visit will be performed. As the DRAGON 1 trial has been categorized as medium risk, monitors will randomly check 25% of the data.

Safety Assessment

All adverse and serious adverse events reported by the subject or observed by the investigator or staff will be recorded both in the Investigator Site File (ISF) and in CASTOR (supplementary paragraph 2). All complications will be categorized using the Dindo-Clavien classification.
A Data Safety Monitoring Board (DSMB) has been set up to guarantee independent evaluation of DRAGON 1 trial patients and to assist and advise Principal Investigators so as to protect the validity and credibility of the trial.

**Discussion**

PVE/HVE is a new and promising percutaneous procedure to increase and accelerate the FLR-hypertrophy before resection with minimal physical impact for patients with primary (supplementary paragraph 5) and metastatic liver tumors.

Currently, new techniques are often implemented on single center level without appropriate scientific assessment. Consequently, data on safety or the indication of the new technique is often based on low quality observational studies and expert opinions. Technique development and safe implementation in consensus among expert centers is ideally required to prevent redundant studies or too liberal application.

The first prospective trial of the DRAGON trials collaboration, the single arm DRAGON 1 trial, aims to assess the safety profile of PVE/HVE in patients with CRLM and small FLR and the accrual potential of each participating center. It enables centers within the collaborative to gain experience based on consensus work instructions of PVE/HVE and consequently allow for safe implementation. Outcomes of the DRAGON 1 trial will be used to determine the effect size required for sample size calculation of the DRAGON 2 randomized controlled trial.

Furthermore, several technical approaches of PVE/HVE and different embolic agents used in PVE/HVE are described in literature. For the DRAGON 1 trial, it was decided in Delphi consensus (supplementary paragraph 3) to not standardize the Portal Vein Embolization procedure since these procedures are well established and, at time of writing the protocol, did not favor one approach over another. It was also decided not to use glue during HVE since glue migration was observed in cases within the collaborative group, albeit without clinical consequences.

To date, to avoid post hepatectomy liver failure, FLR function assessment seems to be more important than FLR volume to proceed with resection. Several modalities to measure total liver function are described, but currently Technetium-99 m (99mTc)-mebrofenin hepatobiliary scintigraphy (HBS) is the only reliable method to provide functional information of the FLR [23–25]. Interpretation of HBS is considered complex and time consuming, but more and more implemented in clinical pathways of major liver oncology centers. Unfortunately, at time of the start of DRAGON trial 1, multiple participating centers had not implemented HBS and only available data on liver function from participating sites performing HBS already is collected. Currently, all participating centers are encouraged to take part in the HBS implementation program, called “DRAGON meets HERCULES.” HBS data will be collected in a subset of centers during future DRAGON trials.

In the randomized DRAGON 2 trial, following the DRAGON 1 trial, in patients with CRLM and Primary liver tumors we will investigate the value of PVE/HVE over PVE alone in a superiority design. FLR hypertrophy, Kinetic Growth Rate, resectability, and survival among other outcomes will be studied.

**Trial Status**

The growing DRAGON trials collaborative consists of more than 60 HPB centers.

The latest approved version of the DRAGON 1 trial protocol in Maastricht is version 4, April 21, 2021. The first informed consent was signed on May 8, 2020. Currently, 39 centers are actively recruiting patients in the DRAGON 1 trial. www.dragontrial.com can be consulted for the latest updates. The last patient will be recruited before July 1, 2022. The final report on the primary endpoint of the DRAGON 1 trial is expected by the end of 2022.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00270-022-03176-1.

**Acknowledgements** The authors acknowledge the contribution of S. Kern1 and the Data and Safety Monitoring Board: J. Melenhorst2, G. Maleux3, and C. Aloman4. Affiliations: 1Department of General and Visceral Surgery, Cantonal Hospital Winterthur, Winterthur. 2Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands. 3Department of Radiology, University Hospitals Leuven, Leuven, Belgium. 4Department of Internal Medicine, Rush University Medical Center, Chicago, United States.

**Author Contributions** After two online Delphi rounds among 30 surgeons and interventional radiologists and a formal investigator meeting the trial protocol was written by R. Korenblik, MD PhD, University of Maastricht. E. Schadde, MD, FACS, FEBS (HPB), Rush University; Chicago C. van der Leij, MD PhD EBIR FCIRSE, Maastricht University Medical Center+R.M. van Dam, MD PhD, Maastricht University Medical Center+.

**Funding** The Dutch Cancer Society (KWF), Maastricht University Medical Center, NIHR, Guerbet, and Abbott Laboratories provided unrestricted financial support for monitoring, coordination and the infrastructure of this trial. All funders do not interfere with the initiation, coordination, analysis, or publication of the results. Maastricht University is the sponsor of the DRAGON 1 trial.

**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.
**Ethics Approval and Consent to Participate** All procedures performed in the DRAGON 1 trial are in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participating centers obtained ethical and local approval by the board of directors (if applicable). For the sponsor site, Maastricht, the METC azM/UM approved this trial (NL7135.068.19 /METC19-078).

**Informed Consent** Informed consent will be obtained from all individual participants included in the study according to Good Clinical Practice guidelines.

**Consent for Publication** For this type of study, study protocol paper, consent for publication is not required.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

**References**

1. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006;24:3939–45.
2. Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg. 2009;250:540–8.
3. van Gulik TM, van den Esschert JW, de Graaf W, et al. Contraversories in the use of portal vein embolization. Dig Surg. 2008;25:436–44.
4. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol. 2013;36:25–34.
5. Shindoh J, Tseng CW, Aloia TA, et al. Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. J Gastrointest Surg. 2014;18:45–51.
6. Kianmanesh R, Farges O, Abdalla EK, Sauvanet A, Ruzsniewski P, Belghiti J. Right portal vein ligation: a new planned two-step all-surgical approach for complete resection of primary gastrointestinal tumors with multiple bilateral liver metastases. J Am Coll Surg. 2003;197:164–70.
7. Jaeck D, Oussouitzoglou E, Rosso E, Greget M, Weber JC, Bachellerie P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004;240:1037–49; discussion 49–51.
8. Wicherts DA, Miller R, de Haas RJ, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg. 2008;248:994–1005.
9. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol. 2011;29:1083–90.
10. Tsai S, Marques HP, de Jong MC, et al. Two-stage strategy for patients with extensive bilateral colorectal liver metastases. HPB (Oxford). 2010;12:262–9.
11. Schadde E, Schnitzbauer AA, Tschuor C, Raptis DA, Bechstein WO, Clavien PA. Systematic review and meta-analysis of feasibility, safety, and efficacy of a novel procedure: associating liver partition and portal vein ligation for staged hepatectomy. Ann Surg Oncol. 2015;22:3109–20.
12. Schadde E, Hernandez-Alejandro R, Lang H, de Santibanes E, Clavien PA. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors. Results of a multicentre analysis: reply. World J Surg. 2015;39:1850–1.
13. Sandstrom P, Rosok BI, Sparrelid E, et al. ALPPS improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a scandinavian multicenter randomized controlled trial (LIGRO Trial). Ann Surg. 2018;267:833–40.
14. Schadde E, Ardiles V, Robles-Campos R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014;260:829–36; discussion 36–8.
15. Schadde E, Tsatsaris C, Swiderska-Syn M, et al. Hypoxia of the growing liver accelerates regeneration. Surgery. 2017;161:666–79.
16. Nagino M, Yamada T, Kamiya J, Uesaka K, Arai T, Nimura Y. Left hepatic trisegmentectomy with right hepatic vein resection after right hepatic vein embolization. Surgery. 2003;133:580–2.
17. Hocquenet A, Sotiriadis C, Duran R, Guiz B, Yamaguchi T, Halkic N, Melloul E, Demartines N, Denys A. Preoperative portal vein embolization alone with biliary drainage compared to a combination of simultaneous portal vein, right hepatic vein embolization and biliary drainage in katskin tumor. Cardiovasc Intervent Radiol. 2018:1885–1891.
18. Schadde E, Guiz B, Deal R, et al. Simultaneous hepatic and portal vein ligation induces rapid liver hypertrophy: a study in pigs. Surgery. 2019;165:525–33.
19. Guiz B, Chevallier P, Denys A, et al. Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique. Eur Radiol. 2016;26:4259–67.
20. Guiz B, Quenet F, Escal L, et al. Extended liver venous deprivation before major hepatectomy induces marked and very rapid increase in future liver remnant function. Eur Radiol. 2017;27:3343–52.
21. Heil J, Korenblik R, Heid F, et al. Preoperative portal vein or portal and hepatic vein embolization: DRAGON collaborative group analysis. Br J Surg. 2021;108:834–42.
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
23. Rassam F, Olthof PB, Richardson H, van Gulik TM, Bennink RJ. Practical guidelines for the use of technetium-99m metrofenin hepatobiliary scintigraphy in the quantitative assessment of liver function. Nucl Med Commun. 2019;40:297–307.
24. de Graaf W, van Lienden KP, Dinant S, et al. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. J Gastrointest Surg. 2010;14:369–78.
25. Dinant S, de Graaf W, Verwer BJ, et al. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. J Nucl Med. 2007;48:685–92.
Affiliations

1 GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht Universiteitssingel 40 room 5.452, 6229 ET Maastricht, The Netherlands
2 Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands
3 Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands
4 Department of General, Visceral and Transplant Surgery, University Hospital Aachen, Aachen, Germany
5 Department of Radiology, University Hospital Aachen, Aachen, Germany
6 Department of General and Visceral Surgery, Cantonal Hospital Winterthur, Winterthur, Switzerland
7 Department of Radiology, Cantonal Hospital Winterthur, Winterthur, Switzerland
8 Department of Radiology, Rush University Medical Center, Chicago, USA
9 Department of Surgery, Rush University Medical Center Chicago, Chicago, USA
10 Department of Surgery, Ospedale San Raffaele, Milan, Italy
11 Department of Surgery, Fondazione Poliambulanze, Brescia, Italy
12 Department of Radiology, University Hospital, Linköping, Sweden
13 Department of Radiology, Maxima Medisch Centrum, Eindhoven, The Netherlands
14 Department of Radiology, Clinic Favoriten, Vienna, Austria
15 Department of Radiology, Bournemouth and Christchurch, The Royal Bournemouth and Christchurch Hospitals, Bournemouth and Christchurch, UK
16 Department of Surgery, CHU UCLouvain Namur, Namur, Belgium
17 Department of Surgery, Biomedical and Clinical Sciences, Linköping University Hospital, Linköping, Sweden
18 Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands
19 Department of Radiology, University Medical Center Groningen, Groningen, The Netherlands
20 Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
21 Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands
22 Department of Surgery, University Hospital Heidelberg, Heidelberg, Germany
23 Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA
24 Department of Radiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Sant’Orsola-Malpighi Hospital, Bologna, Italy
25 Department of Radiology, University Hospital Oslo, Oslo, Norway
26 Department of Surgery, Aintree University Hospitals NHS, Liverpool, UK
27 Department of Radiology, University Hospital Heidelberg, Heidelberg, Germany
28 Department of Surgery, Western Health Footscray, Footscray, Australia
29 Department of Radiology, University Hospital Dr. Josep Trueta de Girona, Girona, Spain
30 Department of Surgery, Royal Prince Alfred Hospital, Camperdown, Australia
31 Department of Surgery, Monash Health, Clayton, Australia
32 Department of Surgery, University Hospital Germans Trias i Pujol, Badalona, Spain
33 Department of Radiology, Aintree University Hospitals NHS, Liverpool, UK
34 Department of Radiology, Monash Health, Clayton, Australia
35 Department of Radiology, Ospedale San Raffaele, Milan, Italy
36 Department of Radiology, CHU UCLouvain Namur, Namur, Belgium
37 Department of Radiology, Amsterdam University Medical Centers Location AMC, Amsterdam, The Netherlands
38 Department of Radiology, Karolinska University Hospital, Stockholm, Sweden
39 Department of Surgery, CHU de Liège, Liège, Belgium
40 Department of Surgery, Amsterdam University Medical Centers Location AMC, Amsterdam, The Netherlands
41 Department of Surgery, Hospital Clinic de Barcelona, Barcelona, Spain
42 Department of Surgery, University Hospital Oslo, Oslo, Norway
43 Department of Surgery, Hospital Parc Taulí de Sabadell, Sabadell, Spain
44 Department of Radiology, Hospital Parc Taulí de Sabadell, Sabadell, Spain
45 Department of Radiology, University Hospital Mútua Terassa, Terassa, Spain
46 Department of Radiology, CHU de Liège, Liège, Belgium
47 Department of Surgery, Gemelli University Hospital Rome, Rome, Italy
48 Department of Surgery, Amphia, Breda, The Netherlands
49 Department of Radiology, Hospital Clinic de Barcelona, Barcelona, Spain
50 Department of Surgery, HPB Center Vienna Health Network, Clinic Favoriten, Vienna, Austria
51 Department of Surgery, Erasmus Medisch Centrum, Rotterdam, The Netherlands
52 Department of Surgery, University Hospital Frankfurt, Frankfurt, Germany
Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.