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Current Perspective

Parenchymal sparing surgery brings treatment of colorectal liver metastases into the precision medicine era



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Abstract The treatment of advanced colorectal liver metastases (CRLMs) follows the biphasic pattern characteristic of oncological surgery. A phase of escalation—the therapeutic aggressiveness—is followed by a phase of de-escalation aimed at decreasing the morbidity, while preserving the gains in survival. From a maximum of three lesions, the rule no longer limits the number, provided the intervention does not cause lethal liver failure. Technically feasible non-anatomical resections, two-stage hepatectomies, portal vein obliteration and so forth, have pushed the boundaries of surgery far. However, the impact and the biology of metastatic processes have been long ignored.

Parenchymal sparing surgery (PSS) is a de-escalation strategy that targets only metastasis by minimising the risk of stimulating tumour growth, while enabling iterative interventions. Reducing the loss of healthy parenchyma increases the tolerance of the liver to interval chemotherapy. Technically, PSS could use any type of hepatectomy, providing it is centred on the metastatic load alongside intraoperative ablation.

The PSS concept sometimes wrongly comes across as a debate between minor versus major hepatectomies. Hence, we propose a clear definition, both quantitative and qualitative, of what PSS is and what it is not. Conversely, the degree of selectivity of PSS as a percentage

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of the volume of resected metastases versus the volume of total liver removed has not been stopped to date and should be the subject of prospective studies.

Ultimately, the treatment of advanced CRLMs, of which PSS is a part, needs to be personalised by the multidisciplinary team by adapting its response to each new recurrence.

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1. Introduction

Treatment of colorectal liver metastases (CRLMs) is a paradigm of the progression of surgical oncology. Initially, conservative techniques were used on a limited number of lesions. Surgeons were cautious owing to the inherent difficulties of liver surgery and the low efficacy of chemotherapy at the time. At the end of the 1980s, it was assumed that no patient operated on for more than four CRLMs would survive beyond 3 years. Nevertheless, this was progressively followed by more aggressive approaches, extending the range of indications for more and more advanced diseases. Finally, indications of resections changed to focus on ensuring enough functional parenchyma remained. In parallel, extrahepatic targets such as limited peritoneal carcinomatosis and lung metastases were included in curative procedures. Owing to the progress in anaesthesiology and perioperative care, surgeons just focussed on what was technically feasible. But finally, inspired by biology and through the usual de-escalation process of surgical oncology, the strategy matured targeting just the liver metastases and sparing the healthy liver parenchyma.

To serve this de-escalation, several techniques, such as non-anatomical resections [1], minor hepatectomies [2] and intraoperative ablations [3], have been used. The oncological clearance also evolved from more than 2 cm to at least 1 cm, then 2 mm and finally to 0 mm [4]. Refined intraoperative ultrasound (IOUS) guidance allowed removal of deeply located liver lesions, as many as 50, in a single operation [5]. IOUS also enabled successful application of intraoperative ablation [6]. Furthermore, the regenerative ability of liver parenchyma presented unique opportunities in surgical oncology. Selective vascular occlusion of the areas with CRLMs made it possible to induce hypertrophy of the future remnant liver (FRL), allowing sophisticated one or two-stage surgical procedures [7] and minimising the risk of postoperative liver failure but increasing, at the same time, the risk of triggering the tumoural growth of remnant micrometastases.

In parallel, all these aggressive and sophisticated treatments were legitimised by improving the systemic control with several lines of chemotherapy and targeted therapy. Indeed, the survival of metastatic patients in the palliative setting has increased from 24 to 29 months [8]. Now, resectable diseases have an overall 5-year

survival of almost 65% for solitary CRLMs [9] and 35% for multisite CRLMs [3]. However, this efficacy pays a price in terms of liver-induced toxicity with increased morbidity and mortality due to extended resections [10].

As surgeons and oncologists faced frequent recurrent disease requiring several lines of treatments, it became critical to take into account the biology of the metastatic process. The risks with concomitant systemic chemotherapy and biologicals need to be considered when defining the optimal type and timing of CRLM surgery. All these criteria are key for the de-escalation strategy that spares normal parenchyma and focus treatment on the sole identified CRLM. Conceptually, this approach brings back oncology to the heart of the discussion. Contrarily, the recent introduction of laparoscopy to treat CRLMs, just because it seems feasible, breaks down the principle of de-escalation by promoting a return to major hepatectomies which are less difficult to perform than tumourectomies.

Nevertheless, authors who support parenchymal sparing surgery (PSS) have published different definitions introducing some confusion [1,11–16]. Considering how this technique can potentially decrease the risk of surgical complications, recurrence and progression, there is a clear possibility today for hepatobiliary experts to reach for a consensus on PSS definition; how PSS should be implemented practically and how quality assurance measures could help us in its rationalisation have still to be discussed and developed.

1.1. Diffusion of micrometastatic CRLMs as the main criticism for extensive resections

From being a lethal disease, the CRLM has become more of a chronic disease [17]. The higher the number of treatment lines that can successfully be completed by patients, the longer the survival. This is true not only for systemic treatments but also for surgery.

Current rationale is that all the metastases are synchronous [18] with the primary tumour. Metachronous metastasis is thought to be a consequence of the failure of the immune surveillance of dormant micrometastatic lesions [18], which are present at an early stage of disease. These might have also infiltrated the FRL segments. Hence, increasing the resection volume is a one-shot strategy that will not necessarily benefit the

patients. On the other hand, PSS is a precision surgical strategy that is adapted to spotting multiple micro-metastases, regardless of their location in the organ. Moreover, it is delivered similar to systemic chemotherapy with several lines tackling several waves of recurrences.

Recent data on immune surveillance confirm the interest for iterative local treatments such as ablation of metastases. Such treatments are supposed to liberate tumour cell-derived antigens leading to autovaccination. Proponents of trials hypothesise that they may be able to increase this abscopal effect (e.g. http://www.eortc.org/research_field/clinical-detail/1560/). Intraoperative ablation, which has been clearly underused in hepato-biliary (HPB) surgery, could now find a fair recognition, especially as a complementary strategy to immune therapy.

It is important for a multidisciplinary team (MDT) to propose several lines of treatment, including iterative surgery for CRLMs during different waves of recurrences [19]. Moreover, choosing chemotherapy regimens that do not significantly increase surgical complications is crucial for the successful control of metastatic disease. It is known that more than 12 cycles of chemotherapy can lead to an unacceptable level of postoperative mortality [2]. PSS permits good outcomes both for minor and major hepatectomies, provided only a small portion of normal parenchyma is resected in both procedures [11].

1.2. Surgical trauma may induce recurrence and progression

It is well established that any type of liver parenchymal trauma—resection, ablation or portal vein obliteration (PVO)—releases cytokines responsible both for hepatocyte homeostasis and the residual metastatic growth [20,21]. It has been clearly shown that PSS advocates one-stage surgery more frequently compared with two-stage surgery [5,22], which may require additional PVO. PSS can offer safe iterative treatment when faced with many recurrences. It also minimises the biological risk of the treatment, a risk clearly identified among patients who drop out of the two-stage procedures because of progression [23,24]. The idea that PVO, two-stage hepatectomies or the associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure can be a test for more aggressive surgery is not acceptable [24] as survival of patients who drop out is lower than that of patients treated by palliative chemotherapy alone [23]. Moreover, a recent analysis has shown that recurrence-free survivals of patients who underwent one-stage surgery are similar to those successfully completed staged approach [24]. European Organisation for Research and Treatment of Cancer (EORTC)/European Society of Surgical Oncology (ESSO) 1409 CLIMB study has recently completed its

primary analysis on 30- and 90-day surgical complication rates in patients with unresectable CRLMs that have undergone either one- or two-stage hepatectomies or surgery for multisite metastases (ASCO 2018 abstract #216587). There is an indication for more severe complications and higher mortality rates for two-stage procedures. Assessment of correlation to tumour burden is ongoing.

ALPPS has been proposed as a better inducer of FRL growth and consequently, as a salvage strategy for advanced CRLMs. This technique induces more parenchymal necrosis and inflammatory cytokine release. Mortality is as high as 9% [25,26], and the oncological outcomes do not seem any better than in palliative treatment [27]. Last but not the least, recent studies indicate that the volume of hepatocytes is not correlated to liver function. 99mTc-mebrofenin scintigraphy shows that post-ALPPS hepatocytes [28] are immature. Consequently, even if FRL volume is obtained, the poorly functioning hepatocytes will increase the risk of postoperative liver failure. One-stage approach assessed preoperatively by an MDT has a clinical and biological superiority over more aggressive approaches such as two-stage hepatectomies, PVO and ALPPS. The risks and benefits of these different techniques should be clearly discussed with patients, at the first instance, or reserved for the more advanced cases [29].

1.3. A challenge to achieve a common definition of PSS

The main misconception regarding PSS is the issue of minor versus major hepatectomies [15,30]. If a right liver is full of CRLMs, a right hepatectomy can be considered as PSS even though it is a major hepatectomy. On the other hand, if a 2-mm CRLM is resected by a full segmentectomy, it should not be considered as PSS even though it is a minor hepatectomy (Fig. 1). The attempt to justify PSS by studying a series of resections for unique metastasis [16] is theoretically correct but clinically distorted; in practice, PSS should be applied for more advanced cases that will need complex decisions

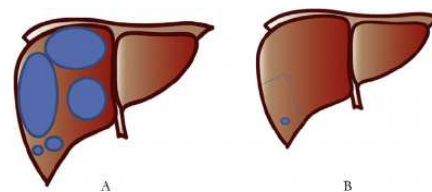


Fig. 1. PSS has no correlation with the classification of minor versus major hepatectomies. (A) illustrates a case of the extended right hepatectomy which is a PSS and (B) illustrates a case of a monosegmentectomy not being a PSS. PSS, parenchymal sparing surgery.

based on a response to chemotherapy and risk of surgical procedure. The authors believe that focussed resection (tumourectomies) [31], even accepting tumour in contact with major vascular structures [32] or the combination of ablation and resection [6], would implement the right concept of PSS. Both approaches minimise the need for a PVO and lower the surgical risk when compared with other procedures.

For a clinical validation of its theoretical superiority, the following questions need to be addressed: what is the practical definition of PSS? How to perform PSS? How can we tailor CRLM surgery to decrease complications yet maintain favourable outcomes? In future, studies evaluating volume-based threshold of an acceptable ratio of normal parenchyma versus the tumoural burden need to be carried out. Is 80% or 50% an acceptable cut-off ratio to judge whether PSS is feasible or not? Will it be possible to correlate this threshold with assessment of clinical and molecular biomarkers, clinical outcomes such as posthepatectomy liver failure frequency or the surgical morbidity/mortality rate? There is no consensus

in these matters yet. Prospective studies on complex CRLMs are scarce, and hence, only retrospective studies [11,15,16,30] have been published based on very different definitions of PSS.

To achieve a common definition of PSS in prospective studies, collaboration across expert networks of surgeons, pathologists, radiologists and oncologists is needed. A standardised data set to accurately and consistently document CRLMs in terms of size, location and extent is needed. Ideally, a central imaging platform is needed to collate images. Preoperative images will need to be correlated with intraoperative findings and postoperative pathology evaluation. A quality assurance infrastructure such as SURCARE [33] can facilitate an integrated central review and correlate clinical outcomes. Fig. 2 shows pathology quality assesment (QA) performed in the EORTC 1527 DREAM study demonstrating standard cuts using a machine slicer and photo documentation of each slice. This approach will offer more accurate estimates of tumour volume and definition of PSS.

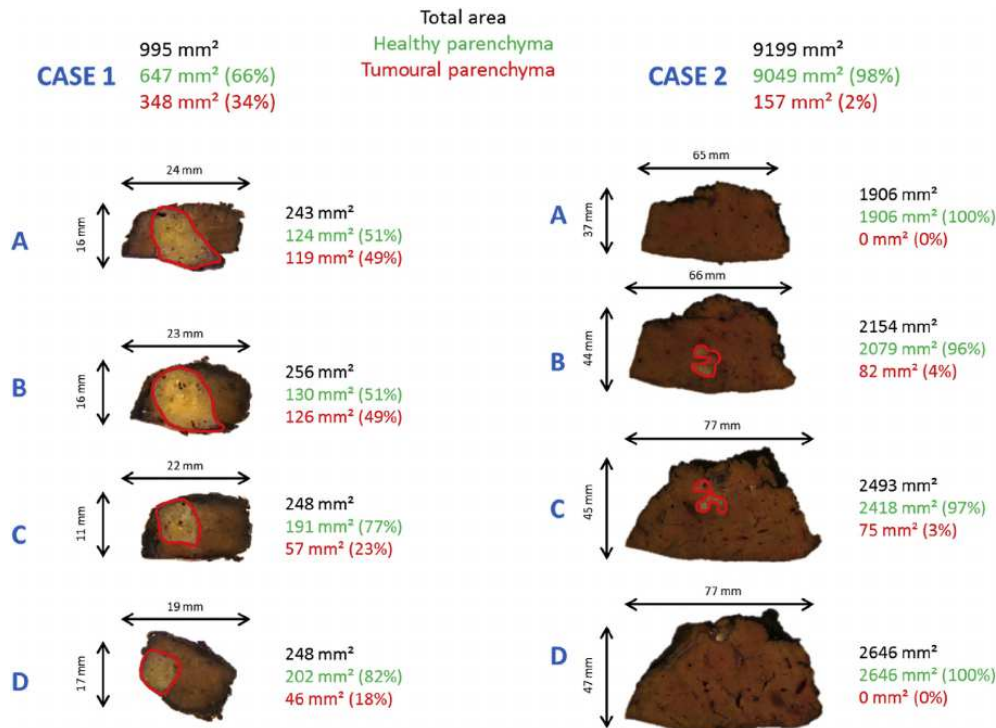


Fig. 2. An example of how a surgical specimen has to be proceeded to appraise if the surgery was a PSS. The specimen is cut into 5-mm slices. The total area and the tumour area are delimited, and software determines the surface of each zone. This operation is performed for each slide. The subtraction of the total area on the surface of the tumour area makes it possible to determine the surface of healthy parenchyma and so the respective percentages of healthy and tumour parenchyma. Case 1 illustrates a PSS when case 2, a non-PSS. PSS, parenchymal sparing surgery.

2. Conclusion: moving towards precision medicine with PSS for better CRLM surgery outcomes

We believe that PSS brings surgical treatment of CRLMs into the personalised medicine era. PSS is tailored around patient’s disease biology and clinical characteristics. It requires surgeons and MDTs to plan treatments with less risk of complications that may trigger recurrences or progression. In the future, tailoring a parenchymal surgery for one patient will also incorporate molecular and clinical scores along with the tumour volume.

The main limitation of PSS is the relevance of the surgical indication itself. Is it relevant to operate on 15, 20, 30 or 50⁵ CRLMs? Probably the answer is personal, case by case and remains the privilege of the MDT decision. It is true that the prognosis of the CRLM disease decreases with the number of metastases and the plurality of the involved organs. Pushing the limits of PSS relegates surgery to an adjuvant role to chemotherapy (which increases the survival of these patients in the palliative setting, year after year). Nevertheless, some noteworthy progress can be expected in CRLM survival in the future, mainly by making microsatellite stable (MSS) colorectal tumours sensitive to immunotherapy (which is currently not the case). Surgeons must be technically ready to assume their role of ‘residual lesion cleaners’.

Another technical limitation is the vanishing and the isoechoic metastases, two subtypes of CRLMs probably responsible for a large amount of recurrences of the disease. At a macroscopic but invisible level, they represent the same threat as micrometastases do at the microscopic level. Alone, this cannot justify sacrificing a large amounts of normal parenchyma. But the debate of removing the putative volume of a missing CRLM versus an imaging survey is always pending and surpasses the debate of PSS.

The first interesting prospective evaluation is expected as a translational research study within EORTC 1527 GITCG (DREAM) study (http://www.eortc.org/research_field/clinical-detail/1527/) in collaboration with EORTC Gastrointestinal Cancer Group, ESSO, Japan Clinical Oncology Group, Ligue nationale contre le Cancer, MD Anderson Cancer Center and Ohio Hospital State University.

Reaching a consensus on PSS will potentially offer a more precise, safe and effective surgery for CRLM patients.

Conflict of interest statement

None declared.

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References

- [1] Gold JS, Are C, Kornprat P, Jarnagin WR, Gonen M, Fong Y, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Ann Surg* 2008;247(1): 109–17.
- [2] Cauchy F, Aussilhou B, Dokmak S, Fuks D, Gaujoux S, Farges O, et al. Reappraisal of the risks and benefits of major liver resection in patients with initially unresectable colorectal liver metastases. *Ann Surg* 2012;256(5):746–52.
- [3] Evrard S, Rivoire M, Arnaud J, Lermite E, Bellera C, Fonck M, et al. Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. *Br J Surg* 2012;99(4):558–65.
- [4] de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg* 2008;248(4): 626–37.
- [5] Torzilli G, Procopio F, Botea F, Marconi M, Del Fabbro D, Donadon M, et al. One-stage ultrasonographically guided hepatectomy for multiple bilobar colorectal metastases: a feasible and effective alternative to the 2-stage approach. *Surgery* 2009;146(1): 60–71.
- [6] Evrard S, Poston G, Kissmeyer-Nielsen P, Diallo A, Desolneux G, Brouste V, et al. Combined ablation and resection (CARE) as an effective parenchymal sparing treatment for extensive colorectal liver metastases. *PLoS One* 2014;9(12): e114404.
- [7] Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann Surg* 2000;232(6):777–85.
- [8] Venook A, Niedzwiecki D, Heinz-Josef L, Innocenti F, Mahoney M, O’Neil B, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). *J Clin Oncol* 2014;32:5s. suppl: abstr LBA3.
- [9] Adam R, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010;252(5): 774–87.
- [10] Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;24(13):2065–72.
- [11] Desjardin M, Desolneux G, Brouste V, Degrandi O, Bonhomme B, Fonck M, et al. Parenchymal sparing surgery for colorectal liver metastases: the need for a common definition. *Eur J Surg Oncol* 2017;43(12):2285–91.
- [12] Donadon M, Cescon M, Cucchetti A, Cimino M, Costa G, Pesi B, et al. Parenchymal-sparing surgery for the surgical treatment of multiple colorectal liver metastases is a safer approach than major hepatectomy not impairing patients’ prognosis: a bi-institutional propensity score-matched analysis. *Dig Surg* 2018;35(4):342–9.
- [13] Lordan JT, Roberts JK, Hodson J, Isaac J, Muiesan P, Mirza DF, et al. Case-controlled study comparing peri-operative and cancer-related outcomes after major hepatectomy and parenchymal sparing hepatectomy for metastatic colorectal cancer. *HPB (Oxford)* 2017;19(8):688–94.
- [14] Matsuki R, Mise Y, Saiura A, Inoue Y, Ishizawa T, Takahashi Y. Parenchymal-sparing hepatectomy for deep-placed colorectal liver metastases. *Surgery* 2016;160(5):1256–63.
- [15] Memeo R, de B V, Adam R, Goere D, Azoulay D, Ayav A, et al. Parenchymal-sparing hepatectomies (PSH) for bilobar colorectal

- liver metastases are associated with a lower morbidity and similar oncological results: a propensity score matching analysis. *HPB (Oxford)* 2016;18(9):781–90.
- [16] Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. *Ann Surg* 2016; 263(1):146–52.
- [17] Van LK, Venook AP. Metastatic colorectal cancer: a curable disease. *Oncology (Williston Park)* 2012;26(3):275–6. 282.
- [18] Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. *Nat Rev Cancer* 2007;7(11):834–46.
- [19] Vigano L, Pedicini V, Comito T, Carnaghi C, Costa G, Poretti D, et al. Aggressive and multidisciplinary local approach to iterative recurrences of colorectal liver metastases. *World J Surg* 2018; 42(8):2651–9.
- [20] Chijiwa K, Saiki S, Tanaka M. Serum interleukin-6 and hepatocyte growth factor levels in patients after hepatectomy. *Hepato-Gastroenterology* 2002;49(44):467–71.
- [21] Elias D, de Baère T, Roche A, Mducreux, Leclere J, Lasser P. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. *Br J Surg* 1999;86(6):784–8.
- [22] Evrard S, Poston G. Response to Faitot et al "Two-stage hepatectomy versus 1-stage resection combined with radiofrequency for bilobar colorectal metastases: a case-matched analysis of surgical and oncological outcomes". *Ann Surg* 2017;265(4): e52–3.
- [23] Brouquet A, Abdalla EK, Kopetz S, Garrett CR, Overman MJ, Eng C, 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(8): 1083–90.
- [24] Vigano L, Torzilli G, Cimino M, Imai K, Vibert E, Donadon M, et al. Drop-out between the two liver resections of two-stage hepatectomy. Patient selection or loss of chance? *Eur J Surg Oncol* 2016;42(9):1385–93.
- [25] Tanaka K, Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): short-term outcome, functional changes in the future liver remnant, and tumor growth activity. *Eur J Surg Oncol* 2015;41(4):506–12.
- [26] Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al. Early survival and safety of ALPPS: first report of the international ALPPS registry. *Ann Surg* 2014;260(5):829–38.
- [27] Wanis KN, Buac S, Linecker M, Ardiles V, Tun-Abraham ME, Robles-Campos R, et al. Patient survival after simultaneous ALPPS and colorectal resection. *World J Surg* 2017 Apr;41(4): 1119–25.
- [28] Truant S, Baillet C, Deshorgue AC, Leteurtre E, Hebbar M, Ernst O, et al. Drop of total liver function in the inter-stages of the new associating liver partition and portal vein ligation for staged hepatectomy technique: analysis of the "Auxiliary liver" by HIDA scintigraphy. *Ann Surg* 2016;263(3):e33–4.
- [29] Evrard S. In favour of one-stage strategy (OSS). *Eur J Surg Oncol* 2015;41(12):1568–9.
- [30] Kingham TP, Correa-Gallego C, D'Angelica MI, Gonen M, DeMatteo RP, Fong Y, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. *J Am Coll Surg* 2015;220(4):471–9.
- [31] Torzilli G, Procopio F, Vigano L, Costa G, Fontana A, Cimino M, et al. The liver tunnel: intention-to-treat validation of a new type of hepatectomy. *Ann Surg* SEP 2017;2017. <https://doi.org/10.1097/SLA.0000000000002509>.
- [32] Torzilli G, Procopio F, Vigano L, Cimino M, Costa G, Del FD, et al. Hepatic vein management in a parenchyma-sparing policy for resecting colorectal liver metastases at the caval confluence. *Surgery* 2018;163(2):277–84.
- [33] Evrard S, Audisio R, Poston G, Caballero C, Kataoka K, Fontein D, et al. From a comic opera to surcare an open letter to whom clinical research in surgery is a concern: announcing the launch of SURCARE. *Ann Surg* 2016;264(6):911–2.