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Review

THE USE OF MACHINE PERFUSION IN SURGICAL ONCOLOGY AND SPLIT LIVER TRANSPLANTATION

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Summary

Hepatobiliary surgical oncology and liver transplantation (LT) surgery have mutually benefited from their technological progresses and technical achievements of the last decade. The application of machine perfusion (MP) to *ex-situ* hepatectomies allows more patients with primary unresectable tumours to have access to radical treatment. Furthermore, the growing need for liver grafts for transplant purpose engaged surgeons in finding new solutions such as liver splitting during dynamic storage through MP to preserve the possibility of two LTs when *in-situ* splitting is not feasible.

Key words: machine perfusion, liver tumours, hepatectomy, liver transplantation, split liver

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INTRODUCTION

The advent of machine perfusion (MP) represented a revolution in liver transplantation (LT). The use of MP, either hypothermic or normothermic, have been proved to restore marginal grafts to a state where they are deemed transplantable and, consequently, allowing the overall donor pool to be expanded [1-3]. More recently, the idea of reconditioning the graft through MP took place. In fact, the perfusion solution can be used as a medium for drugs, antibodies and even cells, to modify the metabolism and physiology of the perfused livers [3].

Hepatobiliary surgical oncology took advantages of progress and achievements in LT. In 1988, Pichlmayr first described the so-called ***ex-situ*** liver resection with complete removal of the liver from the body and resection as a bench procedure, followed by auto-transplantation of the remnant liver [4]. This pioneering procedure was developed to give the best therapeutic option (namely, liver resection [LR]), to those patients affected by liver tumours for which, due to the extension of the lesion or its location close to main vessels, resection using conventional techniques is extremely difficult or even impossible.

MACHINE PERFUSION AND *EX-SITU* LIVER RESECTION

Definitely, *ex-situ* procedure and its variants wouldn't be possible without LT background [5]. A recent meta-analysis on 224 reported patients who underwent *ex-vivo* liver resection and auto-transplantation showed optimal results [6]: for groups with malignant tumours, the 30-day mortalities were 11.3%, and 1-year survivals were 65.0%; when comparing those with malignant versus those with nonmalignant lesions, major surgical complications occurred in 50.0 *vs* 21.0%; p < .001. Moreover, one has to bear in mind that for malignant indication no other curative option were available, at least since the advent of Transplant Oncology.

From a technical point of view, the liver to be resected is approached same as a graft during organ procurement and hypothermic in situ perfusion is needed to preserve liver parenchymal during total vascular exclusion (TVE) phase. The seminal work described the cooling procedure with the initial 10 min perfusion of 8 L of Bretschneider solution (histidine- tryptophan- ketoglutarate = HTK = Custodiol) via portal vein and 200 mL via hepatic artery. Then the perfusion is repeated for about 5 min after the first 30 min and every 60 min of bench resection [4]. During anhepatic phase, temporary portocaval shunt and/or extracorporeal venovenous bypass is required. Over time, the same preservation solutions as in LT have been successfully used and raised even the idea of adding cytoprotective agents, without confirmation of superiority over standard solutions [7-9]. With the spread of the technique in Europe and Japan, variations have been made but one of the main objectives remains the correct preservation of the liver during resection, and MP is the best available technology for this purpose so far.

About 10 years ago, Authors' group demonstrated that *ex-situ* hepatectomy assisted by MP during bench procedure is feasible in porcine model (Fig. 1) [10]. During the last decade, fine-tuning of the procedure led to our current approach with the adoption of hypothermic oxygenated machine perfusion (HOPE). Compared to the classic Pichlmayr procedure, performing bench hepatectomy with HOPE assistance gives much more control over future liver remnant preservation. Our experience shows a good recovery of liver function after auto-transplantation and a safe post-operative course for the patient [11]. Mechanical perfusion of the liver could be use also in the setting of *ante situm* procedure, that's the case with dissection of the suprahepatic inferior vena cava only and hepatectomy performed inside patient's body. In such condition, the efficacy of conventional cold flushing is questionable during prolonged *in-vivo* TVE and given the uncertain hypothermic protection, surgeons may be obliged to rush to avoid parenchymal injury. Authors' group recently published its technical solution for *ante situm* procedure with HOPE assistance (Fig. 2) [12]. In summary, a machine perfusion system (LiverAssist, Organ Assist, Groningen, The Netherlands©) pumps the perfusate into an inflow cannula in the portal vein. Perfusate is either recovered from an outflow cannula in a suprahepatic vein or suctioned from the abdomen and filtered through a cell saver (Fresenius CATS©) before being returned to the device for chilling and oxygenation. The cannula length never exceeds 1.5 m to avoid increase in flow resistance. Celsior (IGL©) is used routinely both for static and HOPE organ preservation for LT (also because of the low potassium content), although several alternative preservation solutions exist. Artery canulation is never performed to avoid vascular intimal injury and reconstruction-related complications. Available data are too sparse to draw a conclusion, but one could postulate that HOPE may be associated with more efficient and widespread diffusion of cold perfusate and oxygen than cold flushing. Hence, MP during

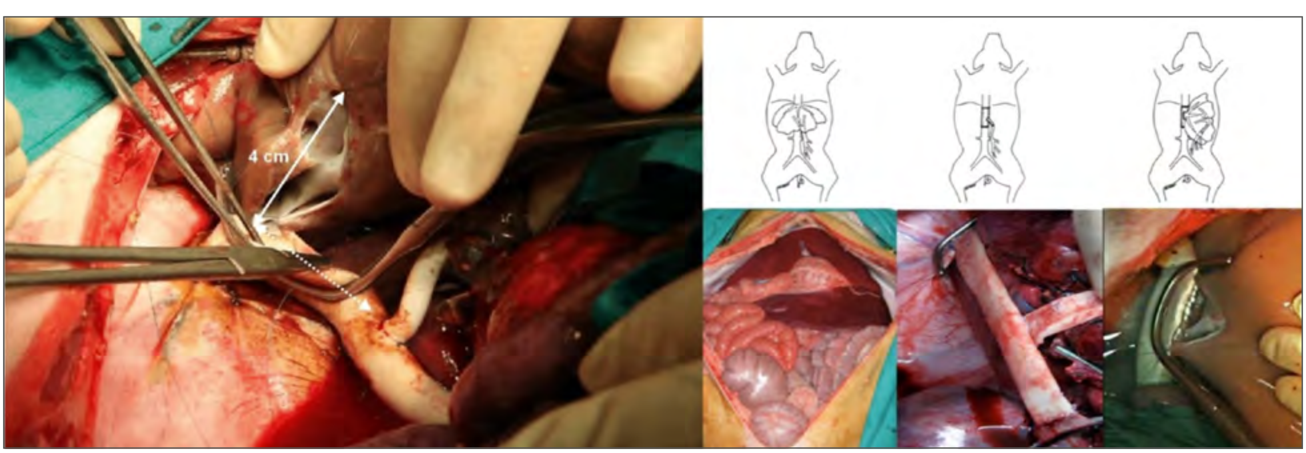

Figure 1. Porcine *ex-situ* liver resection using machine perfusion (Padua experience).

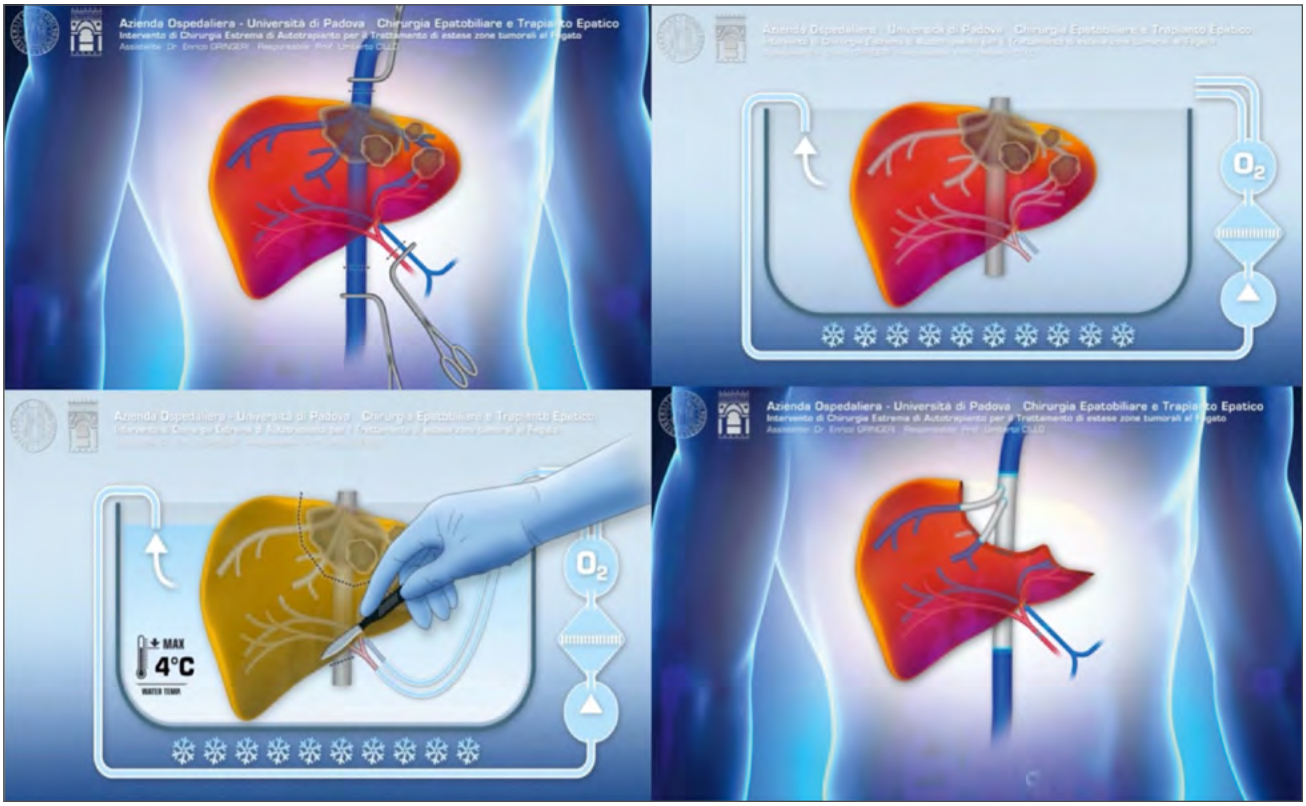

Figure 2. *Ex-situ* liver resection using machine perfusion (Padua experience).

ante situm hepatectomies may extend the benefits seen in LT to the field of surgical oncology.

The fertilization between surgical oncology and transplantation is not only one way.

MACHINE PERFUSION AND SPLIT LIVER TRANSPLANTATION

Technical refinements and technological upgrades (e.g.: ultra-sound dissection devices), in the era of MP, brought new life in the field of *ex-vivo* graft division for transplant purpose, namely split-LT.

Split-LT is an important method that can increase the available donor pool, however split livers are considered marginal grafts *per se* because of their small size and the variable degree of injury incurred due to splitting the liver [13]. *In-situ* splitting, during the warm phase of organ procurement, as several advantages over *ex-vivo*: shorter cold ischemia time, easier identification of the bile duct and vascular tissues, which results in a reduced incidence of bleeding and bile leaks. However, *in-situ* splitting is not always feasible: it depends on local practice and regulations, or donor couldn't tolerate the procedure due to hemodynamic instability. In such cases, *ex-vivo* splitting is the first choice. To mitigate the risks linked to this procedure, it was tested the division of the graft during dynamic oxygenated storage.

Pre-clinical studies on animal model already showed that MP, both normothermic and hypothermic, can be used for liver preservation and splitting, without causing significant graft damage [14-16], and the concept was successfully proved on discarded human liver [17-19]. In 2020, Spada et al. reported the first case of human split-LT during dual hypothermic oxygenated perfusion (DHOPE), and recipients of both extended right graft and hyper-reduced S2 graft experienced neither primary non-function (PNF) nor ischemia-reperfusion injury (IRI) despite prolonged ischemia times of 14 and 11 hours respectively [20].

Early split experiences on discarded livers proposed the use of normothermic machine perfusion (NMP) as a method of viability assessment, logistical improvement, and of potential benefit to the graft by reducing ischemia times. However, liver splitting during NMP may add increased risk of injury through additional rewarming steps, increasing warm ischemia times, even more for extended right lobe grafts traveling to another recipient hospital in static cold storage. Finally, the theoretical advantage of functional testing during NMP is not necessary for high-quality grafts such as the ones that are eligible for splitting. Indeed, HOPE has been preferred in subsequent human case reports [21-23]. Rossignol et al. [24] report the first long series of prospectively performed *ex-situ* liver splitting during HOPE (HOPE-Split).

All partial grafts obtained after HOPE-Split were successfully transplanted with a 90-day graft and recipient survival of 100%. Compared to standard split, registered liver graft-related adverse events (LGRAEs) were similar. Finally, HOPE-Split did not increase split procedure duration but resulted in reduced static cold storage duration leading to reduced IRI on reperfusion biopsies [24].

With the aim of technical standardization of HOPE-Split procedure, Authors agree with Rossignol et Al. that single portal perfusion would be preferable over DHOPE. Portal perfusion alone is easier to perform and allows to remove one of the partial grafts from the device without interrupting the perfusion of the contralateral partial graft, no data support the additional benefit of a dual perfusion compared with a single perfusion [25], and cannulation of the branches of the hepatic artery might expose to arterial injury (increased risk of intimal dissection).

CONCLUSIONS

In conclusion, the use of MP is revolutionizing both the field of surgical oncology and split-LT allowing more and more patients to have access to radical treatment for liver tumours and end-stage liver disease.

Furthermore, MP is functional in the current time of Transplant Oncology in the perspective of logistic organization of recipients for non-HCC indications. Pre-LT abdominal inspection and frozen section analysis of hilar lymph nodes are mandatory in transplant protocols for both cholangiocarcinoma and colorectal liver metastases. Hence, hepatectomy time is inevitably increased or, in the worst scenario, recipient might be changed because of finding of extra-hepatic spreading of the disease. Dynamic storage of graft allocated to such recipients have to be preferred over static, allowing the best graft preservation, and reconditioning in cases of expected prolonged ischemia time [2,26-28].

Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

EG, JL: wrote the paper; FED, DB, RB, AB, AD, SC: performed the literature review; CM, PF, PB, UC: critically revised the paper.

Ethical consideration

This is a review paper. For each study cited in the text the research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

References

1 Schlegel A, Porte R, Dutkowski P. Protective mechanisms and current clinical evidence of hypothermic oxygenated machine perfusion (HOPE) in preventing post-transplant cholangiopathy. J Hepatol 2022;76:1330-1347. https://doi.org/10.1016/j.jhep.2022.01.024

2 Knijff LWD, van Kooten C, Ploeg RJ. The effect of hypothermic machine perfusion to ameliorate ischemia-reperfusion injury in donor organs. Front Immunol 2022;13:848352. https://doi.org/10.3389/fimmu.2022.848352

3 Parente A, Osei-Bordom DC, Ronca V, et al. Organ restoration with normothermic machine perfusion and immune reaction. Front Immunol 2020;11:565616. https://doi.org/10.3389/fimmu.2020.565616

4 Pichlmayr R, Bretschneider HJ, Kirchner E, et al. Ex-situ operation an der leber eine neue möglichkeit in der leberchirurgie. Langenbecks Arch Chir 1988;373:122-126. https://doi.org/10.1007/BF01262775

5 Raab R, Schlitt HJ, Oldhafer KJ, et al. Ex-vivo resection techniques in tissue-preserving surgery for liver malignancies. Langenbeck's Arch Surg 2000;385:179-184. https://doi.org/10.1007/s004230050262

6 Zawistowski M, Nowaczyk J, Jakubczyk M, et al. Outcomes of ex-vivo liver resection and autotransplantation: a systematic review and meta-analysis. Surg (United States) 2020;168:631-642. https://doi.org/10.1016/j.surg.2020.05.036

7 Yamanaka N, Okamoto E, Furukawa K, et al. Hepatic resection under in situ hemihepatic hypothermic perfusion with hepatoprotective agents. Hepatogastroenterology 1995;42:1-4.

8 Lamesch P, Raygrotzki S, Kehrer G, et al. In-situ protection of the liver with Bretschneider HTK solution. Langenbecks Arch Chir 1991;376:85-92. https://doi.org/10.1007/BF01263465

9 Erhard J, Lange R, Scherer R, et al. Comparison of histidine-tryptophan-ketoglutarate (HTK) solution versus University of Wisconsin (UW) solution for organ preservation in human liver transplantation. A prospective, randomized study. Transpl Int 1994;7:177-181. https://doi.org/10.1007/BF00327084

10 Gringeri E, Polacco M, D'Amico FE, et al. A new liver autotransplantation technique using subnormothermic machine perfusion for organ preservation in a porcine model. Transplant Proc 2011;43:997-1000. https://doi.org/10.1016/j.transproceed.2011.01.139.

11 Gringeri E, Auricchio P, Perin L, et al. A translational approach to standardization of machine perfusion adoption in

ex-vivo liver resection. Ann Surg Oncol 2020;27:1919. https://doi.org/10.1245/s10434-019-08163-4

12 Cillo U, Furlanetto A, Nieddu E, et al. Ante situm liver surgery using machine perfusion liver preservation: pilot human experience. Br J Surg 2021;108:e235-e236. https://doi.org/10.1093/bjs/znab095

13 Andrassy J, Wolf S, Lauseker M, et al. Higher retransplantation rate following extended right split-liver transplantation: an analysis from the eurotransplant liver follow-up registry. Liver Transpl 2018;24:26-34. https://doi.org/10.1002/lt.24980

14 Zhang Z-B, Gao W, Liu L, et al. Development and assessment of normothermic machine perfusion preservation for extracorporeal splitting of pig liver. Ann Transplant 2017;22:507-517. https://doi.org/10.12659/aot.904483

15 Zhang Z-B, Gao W, Liu L, et al. Normothermic machine perfusion protects against liver ischemia-reperfusion injury during reduced-size liver transplantation in pigs. Ann Transplant 2019;24:9-17. https://doi.org/10.12659/AOT.910774

16 Ishii D, Matsuno N, Gochi M, et al. Applicability of hypothermic oxygenate machine perfusion preservation for split-liver transplantation in a porcine model: an experimental study. Ann Transplant 2020;25:e919920. https://doi.org/10.12659/AOT.919920

17 Stephenson BTF, Bonney GK, Laing RW, et al. Proof of concept: liver splitting during normothermic machine perfusion. J Surg case reports 2018;2018:rjx218. https://doi.org/10.1093/jscr/rjx218

18 Brockmann JG, Vogel T, Coussios C, et al. Liver splitting during normothermic organ preservation. Liver Transpl 2017;23:701-706. https://doi.org/10.1002/lt.24693

19 van Leeuwen OB, Fujiyoshi M, Ubbink R, et al. Ex-situ machine perfusion of human donor livers via the surgically reopened umbilical vein: a proof of concept. Transplantation 2019;103:2130-2135. https://doi.org/10.1097/TP.0000000000002615

20 Spada M, Angelico R, Grimaldi C, et al. The new horizon of split-liver transplantation: ex-situ liver splitting during hypothermic oxygenated machine perfusion. Liver Transpl 2020;26:1363-1367. https://doi.org/10.1002/lt.25843

21 Thorne AM, Lantinga V, Bodewes S, et al. Ex-situ dual hypothermic oxygenated machine perfusion for human split liver transplantation. Transplant Direct 2021;7:e666. https://doi.org/10.1097/TXD.0000000000001116

22 Mabrut J-Y, Lesurtel M, Muller X, et al. Ex-vivo liver splitting and hypothermic oxygenated machine perfusion: technical refinements of a promising preservation strategy in split liver transplantation. Transplantation 2021;105:e89-e90. https://doi.org/10.1097/TP.0000000000003775

23 Rossignol G, Muller X, Mohkam K, et al. Full left/full right liver graft ex situ split during hypothermic oxygenated perfusion. Pediatr Transplant 2022;26:e14284. https://doi.org/10.1111/petr.14284

24 Rossignol G, Muller X, Hervieu V, et al. Liver transplantation of partial grafts after ex-situ splitting during hypothermic oxygenated perfusion – the HOPE-Split pilot study. Liver Transplant 2022:1-12. https://doi.org/10.1002/lt.26507

25 de Vries Y, Brüggenwirth IMA, Karangwa SA, et al. Dual versus single oxygenated hypothermic machine perfusion of porcine livers: impact on hepatobiliary and endothelial cell injury. Transplant direct 2021;7:e741. https://doi.org/10.1097/TXD.0000000000001184

26 Liew B, Nasralla D, Iype S, et al. Liver transplant outcomes after ex vivo machine perfusion: a meta-analysis. Br J Surg 2021;108:1409-1416. https://doi.org/10.1093/bjs/znab364

27 Lai Q, Ruberto F, Pawlik TM, et al. Use of machine perfusion in livers showing steatosis prior to transplantation: a systematic review. Updates Surg 2020;72:595-604. https://doi.org/10.1007/s13304-020-00797-4

28 Zhang Y, Zhang Y, Zhang M, et al. Hypothermic machine perfusion reduces the incidences of early allograft dysfunction and biliary complications and improves 1-year graft survival after human liver transplantation: a meta-analysis. Medicine (Baltimore) 2019;98:e16033. https://doi.org/10.1097/MD.0000000000016033