Chapter 1

New Surgical Strategies for Bilobar Liver Metastases: One Stage Hepatectomy, Two Stage Hepatectomy and ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy)

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Abstract

In recent decades, the surgical approach in patients with liver metastasis has seen substantial changes. The encouraging results in terms of survival after surgical resection, especially for colorectal histology, led to more interventionist attitude, widening indications and bringing more and more patients to curative treatments. Moreover, the technological advancement of surgical devices and the improvement of imaging techniques has made liver surgery safer and more feasible. But, in the most complex cases the attempt to perform surgical curative resections often collided with the inability to preserve an appropriate post-operative volume, necessary to avoid postoperative hepatic failure. In fact the management of liver cirrhosis or small size hepatic remnant still remains a challenge.

Currently post-hepatectomy liver failure is the major cause of death after liver resection often associated with sepsis and ischemia-reperfusion iniury. In recent years, surgeons around the world have been working to develop new strategies to overcome this limit. Several methods have been proposed for preventing postoperative hepatic failure both in the preoperative, perioperative and postoperative management. Since the introduction of the preoperative portal embolization proposed by Makucchi in the 80's giant steps have been made.

To date in order to limit the damage to parenchyma and to optimize regenerative hepatic capacity many technical considerations have been taken into account.

The purpose of this chapter is to describe the new surgical attitudes regarding the treatment of bilobar liver metastases, focusing on surgical techniques that at present seem to be more effective.

In addition to the technical description, a comparison of the various procedures was carried out to demonstrate the feasibility and possible limits.

Introduction

The liver is a common site of metastases from malignant tumors of gastrointestinal tract and about 50-60% of liver tumors have a secondary origin with over 50% of patients with colorectal cancers who will develop liver metastases during the course of disease [1,2].

Although in the last decades the improvement in surgical techniques, chemotherapy and biological therapies has led to more favorable prognostic results with survival rates ranging prior from 23 to 45 % increasing to almost 60% more recently, a large portion of these patients still die for this disease [3-8].

Besides the encouraging results obtained in terms of survival in the surgical treatment of metastatic colorectal and neuroendocrine cancers [9-13] has prompted the surgeon to an increasingly aggressive attitude towards this

disease. Surgery with radical intent is considered to be the focal point in the treatment of patients suffering from colorectal cancer liver metastases, being the only treatment associated with chemotherapy that can significantly improve survival.

The role of surgery in this context is becoming increasingly important and the indications for surgical intervention in advanced disease are expanding. To date liver surgery for colorectal metastases or neuroendocrine tumors has undergone radical development and gained widespread acceptance, becoming a safe procedure and performed in selected center on a daily basis.

On the other hand surgical approach to hepatic metastases from noncolorectal ,nonneuroendocrine origins is still debated, but several studies in literature show how in selected patients surgery is the best therapeutic strategies able to improve significantly the prognosis when compared to chemotherapy alone [14-16].

The need to perform a surgery with radical intent in many cases conflicts with the impossibility of recruiting patients for resection for the extension of bilobar disease that is too advanced to predict a radical resection, in fact only about 15-25 % of patients with colorectal metastases at the time of diagnosis is eligible for primary liver resection [17].

Moreover the large surgical limit in patients with extensive bilobar liver metastases is due to the necessity to

preserve an adequate proportion of liver parenchyma after resection, in order to avoid the risk of postoperative liver failure (PLF) [18].

Actually it is collegially recognized that the remaining liver percentage after resection is >25% in patients with healthy liver and > 40% in those with cirrhosis, cholestasis or previous chemotherapy treatment [19,20].

Knowledge of the segmental and sub-segmental liver anatomy and hepatic regeneration has expanded markedly, ability to evaluate the functional reserve has improved, and new surgical instruments and procedures have been introduced to evaluate it [21].

The present purpose is to minimize the chance of postoperative hepatic dysfunction using strategies aimed to induce hypertrophy of the future remnant liver (FLR), in order to increase the safety of resection [22].

An extensive liver resection is frequently required to achieve a radical resection (R0), it is evident that the safety of this procedure conflicts with the inability to preserve in many cases a sufficient post-operative liver parenchyma. PLF is the most common cause of mortality after an extended hepatectomy, so PLF is the biggest obstacle faced by hepato-biliary surgeons [23].

In the last three decades the purpose of hepatic surgeons around the world has been to develop and implement a series of tools to induce hypertrophy in the future remnant liver to avoid PLF.

In the 1980s Makuuchi [24] introduced the concept of portal vein embolization (PVE); this technique involves the embolization of the right portal branch in order to induce hypertrophy in the left lobe, enabling a safer removal of large or multiple tumors, mostly located in the right hemiliver and segment IV. This procedure was rapidly adopted by many surgeons to prevent liver failure after a variety of extensive right-sided hepatectomies [25,26].

The next advances of technique were proposed about 10 years later by the surgical team of Paul Brousse hospital in Paris with the introduction of sequential surgical procedures, referred " two-stage hepatectomy (TSH)" to stepwise remove multiple liver tumors, with the aim of allowing the liver to regenerate between both procedures [27].

Although at first the technique did not foresee in all cases the embolization of the right portal branch, the further evolutions with the routine use of portal embolization after the left lobe surgical cleansing, allowed a higher rate of hypertrophy with a safer curative right or extended-right hemiepatectomy [28]. Subsequently the group from Zurich modified this approach by proposing concomitant ligation of a portal right vein (PVL) with the resections of all left-sided tumors during the first surgery, followed a few weeks later by an extended right hepatectomy [29].

The rationale behind this change is that the portal vein ligation is easy to perform during the first surgical

step with the left liver surgical cleaning and leads to a rate of regeneration even greater than PVE [30].

In many cases those developments led to a more curative resection of bilobar metastases, which could not been surgically removed without, but the drawback of these techniques is a long time to achieve hypertrophy between the two surgical step that leads in about 19-28% of cases to a disease progression and therefore to the impossibility of being enrolled for the second surgical stage [27,28,31,32]. This results in the failure of the treatment. Other shortcomings included the insufficient hypertrophy of a putative remnant liver, preventing curative resection or, if performed, leading to postoperative failure due to "*small for size*" syndrome.

Recently to overcome the problems mentioned above, this technique has been modified by performing a portal vein ligation with a "split in liver" during the first stage; in 2012 Schnitzbauer et al.[33] described a this novel approach: "Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy" (ALPPS). This technique resulted in a 74% increase in the volume of the liver remnant, vastly reduced the interval between two surgical step with a completion rate of 100%. ALPPS leads to faster liver hypertrophy rate in 7-14 days [34,35] when compared to TSH which has an average of 99 days (range: 32-210 days) to reach the desired result before the second surgery [36].

Initially, the major controversies to the technique were due to the high rate of morbidity and mortality, reported in about 68% and 14% respectively by Schnitzbauer [33]. Although so many advances and refinements of the initial technique have been made in the last years with a reduction in complications, ALPPS continues to cause heated controversy.

One-Stage Hepatectomy

In the surgical treatment of bilobar metastases from colorectal cancer, the two-stage hepatectomy approach is commonly used. This method allows to extend the surgical indication to patients judged initially inoperable and leads to a higher rate of curative resections, but this approach have some drawbacks. Primarily, patients underwent two surgical procedures and each of which is associated with morbidity and mortality. Secondly, not all patients underwent the first intervention can also be subjected to the second surgical step for progression of the disease occurring in the time elapsed between the two procedures.

A possible alternative was proposed by Torzilli et al. [37] ; they showed how both for primary or metastatic liver tumors a well-defined policy of ultrasonically guided hepatectomy allows to carry out radical operations safely and without major removal of liver parenchyma in the vast majority of patients. This group demonstrated how one-stage hepatectomy (OSH) can be performed even

in the presence of a complex tumor presentation such as multiplicity and vascular invasion [38,39]. The aims of this technique was to establish a surgical procedure that maximizes parenchymal-sparing and allows curative resection in one stage.

After a preoperative imaging with ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI), and chest spiral CT for every patients, the technique uses a very accurate intraoperative ultrasound (IOUS) also with specific contrast agent to identify the relationship between tumor lesions and liver vascularization. The hepatic vessels were spared if it is detectable by IOUS a thin layer of liver parenchyma even if <5 mm from neoplastic lesion, if the portal branch was in contact with metastases without vessel wall discontinuation and without proximal bile duct dilation in order to preserve liver vascular "*scheleton*"; in all the other conditions vessel resection was carried out [37].

The technique leads to minimizing the loss of healthy parenchyma that normally occurs during a major hepatectomy, extending the resection as close as possible to the neoplastic lesion. This inevitably leads to obtain surgical disease-free margins in many cases of the order of 1 mm or less. In fact the main criticism to OSH could be the high proportion of patients receiving a resection with surgical margin with microscopic neoplastic infiltration (R1 resection) [40].

It is widely shown that an adequate disease-free surgical margin is essential to provide to patients an effective neoplastic treatment; but actually especially as regards colorectal liver metastases, the surgeon's approach was to move towards a progressive reduction in surgical margins, which ranged from 1 cm to 1 mm. This is to allow a higher degree of resectability and at the moment a negative surgical margin is the current standard [41].

The use of intraoperative ultrasound maximizes the possibility of getting closer to the tumor by precisely defining the margins. In fact, in the past decades some studies that compare ultrasound-guided resections with those performed without ultrasound guide demonstrated any neoplastic residue on the surgical margin in patients underwent ultrasound-guided resection [42,43].

Moreover, the complexity of these resections often requires that R1 resection is needed, especially when the lesion is located near a vessel. Vessel detachment (R1 vascular margin) is mandatory in many circumstances to avoid greater resection that would result in a higher rate of non-resectable patients for possible PLF.

In this regard Viganò et al. [41] showed how R1 vascular resection can be considered in terms of outcome comparable to parenchymal R0 resection. They claimed that R1 vascular resection guaranteed the same local control of the disease as compared to parenchymal R0 resection, confirming the hypothesis that neoplastic contact with the vessel walls limits neoplastic spread.

A recent multicenter study [40] compared patients underwent two stage hepatectomy with patients in whom performed one stage hepatectomy to elucidate if drop-out (patients not achieving the second stage) of TSH is a patient selection or loss of chance. The patients were matched to have similar tumor features. The manuscript reported a similar outcomes for the two surgical procedures and postulated that drop-out of TSH may be a loss of chance rather than a patients selection. Unselected patients whom underwent to OSH has a same outcomes as selected patients who completed the TSH with similar survival and recurrence rates.

Another point in favor of the surgical technique proposed by Torzilli [37] is the high level of lesions identified intraoperatively that it is reported up to 42% of the metastases removed, which had not been identified by preoperative instrumental examinations. Since surely it deserves a reflection.

Evaluated the oncological efficacy of the OSH compared with the most well-established two stage hepatectomy, some limitations should be highlighted: first of all, the technique involves an adequate preparation of the surgeon on the use of intraoperative ultrasound imaging, since without a correct training it is difficult to perform such complicated interventions.

The fact that the technique involves multiple combined procedures with the aid of ablative techniques

also leads to longer duration of surgery and long vascular clamping times, leads to anesthesia risk and a greater chance of alteration of liver function on the first postoperative days [44]. Although these possible causes of morbidity are in part negligible, reduced liver flow by vascular clamping minimizes the rate of perioperative transfusions with beneficial effects on long and short term outcomes [45,46]. Finally the cost of state of art ultrasound equipment is not entirely negligible.

In conclusion, the technique, albeit with the aforementioned limits, appears to be a valid alternative to TSH and can overcome some of the limitations and consequences of a 2-stage approach.

Two-Stage Hepatectomy

Two-stage hepatectomy (TSH) has been developed as a surgical strategy for extremely complicated cases of bilobar metastatic liver disease in order to achieve a curative R0 resection. The main principle of this approach is a sequential resection by a two-staged liver surgery, its goal is to perform a complete metastasectomy in those cases in which a major resection in a single time would have left a FLR too small for patients survival. The success of this approach is dependent on regeneration of liver tissue after the first stage. Experiments performed almost a century ago suggested that selective occlusion of the portal branch causes atrophy of the ipsilateral liver lobe and hypertrophy of the contralateral lobe [47]. Portal vein emboliza-

tion and portal vein ligation are procedures used in order to increase the size of the future liver remnant before major hepatic resection. A significantly greater volume of FLR correlates with improved synthetic function and thus enables a reduction in the risk of postoperative liver failure. In the late 1980s, Makuuchi et al. first used the selective occlusion strategy in patients in order to extend the limits of liver resection [24].

The technique includes a first stage in which FLR (the less affected lobe that will be designated the future liver remnant, usually the left lobe) is resected by either wedge resections and/or ablation. Portal vein ligation may be performed during the first stage otherwise portal vein embolization can be performed after the first operation to induce hypertrophy of the future liver remnant [36].

PVE stimulates the proliferation of hepatocytes as well as the growth of occult metastases located in the non-embolized hemiliver, as a consequence, progression of liver metastases in the remnant liver could preclude the achievement of a curative liver resection; for this reason metastasectomy in the future liver remnant should come first PVE. In the most of liver units PVE is usually planned two weeks after the first surgical stage. The second-stage operation will then be performed most commonly with an hepatectomy of the more affected contralateral lobe. The success of this method relies on liver regeneration between the two interventions, allowing the second surgical step to

be performed with a lower risk of PLF. The optimal time interval before performing the second liver resection has not yet been clarified and is currently calculated based on the rate of liver regeneration and the control of remnant liver tumors with CT scan (mean time 30-50 days after PVE) [48]. Although portal occlusion (PVE or PVL) can increase the volume of the FLR by up to 40%, the second stage of the procedure was not always performed [48,49]. Some authors reported a drop-out rate ranging from 22-28% [31,32], in most cases, the second surgical stage is abandoned for the presence of disease progression in a short time or for insufficient liver regeneration.

The rate of patients who can be enrolled in the second stage is about 76% with a range from 64% to 87% [50,51], as mentioned above the most frequent cause of not completion of the procedure is progression of disease that is present in 13-35% of patients, in a less part of patients two stage hepatectomy can't be performed for inadequate liver regeneration (0-4%) or for poor condition of patient (3%) [52-55]. Patients who did not complete two stage had extremely unfavourable prognosis with a median survival of 20.4 months compared to those underwent second surgical stage (median survival 56.8%).Three- and 5-year survival rates were 68% and 49%, respectively, for patients who underwent second-stage resection and 6% and 0%, respectively, for patients who did not [56-58].

Regard postsurgical morbidity Passot et al. [56] reported a rates of major complications of 26% after the sec-

ond surgical stage and of 6% for the first. 90-day mortality after second surgery was 7%.

Some authors highlighted how several features on FLR can be considered as negative prognostic factors, as regard the study of Narita et al. [54] showed how the presence of three or more metastases in FLR is an independent risk factor for the failure to achieve the second stage leading to a progression of disease and formation of "*de novo*" metastases in the remnant liver.

Several experimental studies suggested that an alteration hypoxia-induced of tumor microenvironment leads to increased production of vascular endothelial growth factors (VEGF), which can stimulate beyond liver regeneration the growth of dormant micrometastases [59]. Transient hypoxia generated by PVE in non-embolized hemiliver could explain the rate of progression of disease observed [60].

In consideration of this, patients enrolled for the procedure should receive an interval chemotherapy in order to control tumor progression while awaiting the regeneration of FLR, this is also based on initial observations that showed how in patients who did not underwent to an interval chemotherapy a second-stage hepatectomy became impossible [28]. The actual administration of the interval chemotherapy is mandatory [54].

Currently TSH should be considered in selected pa-

tients with bilobar colorectal liver metastases in which a right hepatectomy would leave more than three metastases or any metastasis of more than 3 centimeters in the FLR [61].

In conclusion TSH combined with chemotherapy and timed PVE achieved good results in terms of long-term survival and morbidity with acceptable mortality, but selection criteria for chemotherapy regimens during TSH have not yet been well defined and further clinical trials will be needed to improve the usefulness of the procedure.

ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy)

The rate of patients not meeting the second stage reflects the two-stage hepatectomy limits, mostly for the progression of disease occurring within the longest time needed to achieve an adequate hypertrophy in the future liver remnant. Recently, to overcome these limits in attempt to bring more patients to radical resection, a new surgical approach was proposed with an acronym ALPPS (*Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy*). It represents an evolution of two-stage hepatectomy. This technique has led to an increase of 74% in the volume of the FLR in a mean period of 9 days and greatly reduced the time between the two surgical procedures with a completion rate close to 100% [33],

offering a chance to patients with otherwise irresectable tumors.

ALPPS is typically applied to those patients with very low FLR and may be offered to patients without adequate FLR after embolization of the portal branch or in patients without an initial surgical indication with other techniques [62].

The procedure involves two surgical stage: during exploratory laparotomy the liver tissue was assessed macroscopically and general resectability was defined on the basis of a tumor-free left later liver lobe. The liver is mobilized through the section of falciform, triangular and coronary ligaments and the cava vein is exposed with the relevant hilar structures. Furthermore the assessment of resectability is evaluated and confirmed with intraoperative ultrasound and the positioning of the tumor in relation with vessels. The right portal vein branch is identified and sectioned, the right liver lobe is mobilized and parenchymal transection in situ are performed. All portals , arterial and biliary branches for segment IV° are divided along the rim of the round ligament. Finally, a the right lobe is covered in a plastic bag to prevent any post-operative adhesions and the abdomen is closed [33]. Usually after an interval of 7-14 days [63] patients undergo to a CT hepatic volumetry and the second surgical stage is performed to complete the resection with the ligation of the

right artery, right bile duct and the right hepatic vein [33].

The technique was first performed in 2007 by Schlitt [64] in Regensburg (Germany) and presented to a German Congress in 2010, but was formally described later in 2011 by Lang from Mainz (Germany) in a series of 3 cases on a poster presented during the Ninth European-African Hepato-Pancreatico-Biliary Association Congress in Cape Town, South Africa [65]. In the same year a group of surgeons from Argentina adopted this new technique and reported their initial experiences [66]. ALPPS was first described in a scientific publication in Annals of Surgery in 2012 by Schnitzbauer et al. [33]: they described the first series of 25 cases, the study reported an increased percentage of FLR of 74% in 9 days, so more rapid and effective than normally occurs with the techniques of vascular occlusion (14-42 days with an hypertrophy rate until 40%) [67].

Therefore, ALPPS offers a solution for the two major limitation of PVE and TSH: failure to achieve the desired hypertrophy, long time to reach it and the high drop-off rate following the progression of the disease. Failure to complete the second stage in TSH leads to a really poor prognosis that is lower than patients treated only with chemotherapy, hence outlines the importance of completing the two stage procedures [54,68].

The rationale that animated the Regensburg's group in proposing this new approach is based on the fact that liver

transection leads to an interruption of possible collateral vessels between the two portions of hepatic parenchyma, amplifying the effect of the portal overflow to the FLR hindering recanalization of embolized portal branches. It may be explained with the impressive effect on liver regeneration.

The study of Knoefel et al. [69] compared a rate of parenchymal hypertrophy in series of 22 patients underwent isolated PVE (12 patients), ALPPS (7 patients) and combined procedures (3 patients) , they reported a mean volume increase by 63% after 3 days in patients underwent ALPPS with a volume gain of 22% per day, significantly higher than the group treated with PVE alone. Moreover, the Authors stated that the procedure may be considered in patients who did not step into adequate hypertrophy after portal vein embolization.

Also with regard to neoplastic progression on the "non-embolized" liver in the interval between the portal embolization and second surgery, fact demonstrated by some Authors [70], ALPPS seems to partially obviated the problem by greatly reducing the waiting time to complete the procedure.

Another point in favor of the ALPPS is the possibility of avoiding neoplastic infiltration of FLR, especially in the presence of lesions adjacent to major vascular structures that should otherwise be sacrificed in case of infiltration or encasement [71].

Past Authors emphasized that the feasibility of achieving tumor resection appears to be the most significant advantage of ALPPS. To date analysis of international ALPPS registry showed a completion rate near 100% on 553 patients from 84 centers around the world [72].

On the other hand the procedure has raised many criticisms for the high morbidity and mortality rate shown in the first case studies. Schnitzbauer [33] reported a morbility of 64% and a mortality of 12% ,while Knoefel [69] showed that only two of 7 patients had a course free of complication.

The major complications are due to septic events supported by the presence of bile leak and largely by the necrosis of the IV° liver segment [23,73]. Although initial data could be discouraged to the use of this technique, ALLPS have not been abandoned and these disadvantages have led to a technical review. In fact a recent work of Hernandez-Alejandro et al. [74] reported a reduction in morbidity rate of 36% and a 90-day mortality rate of 0%. The achievement of these results is due to a revision of the technique by the Authors who avoid dissection of the structures of the hepatoduodenal ligament and the saving of the vascular and biliary afferences to the IV° hepatic segment. In recent years many other Authors proposed further technical revisions in an attempt to make ALPPS more safety : totally laparoscopic [75], hybrid [76], partial [77], anterior approach [78], left, rescue, right ALPPS

[79] and satisfactory results were achieved. These surgical changes, in addition to a careful assessment of patient recruitment based on neoplastic biology in accordance to chemotherapy response, may result in a reduction in mortality and morbidity rate.

Beyond the flexibility of the technique the validation of such extreme surgical procedure should be supported by significant oncological findings. At present also due to the limited follow-up of this new procedure, long-term oncological outcomes remain unknown.

The promising short-term results obtained are difficult to translate oncologically, because of the heterogeneous group of patients with different underlying pathologies, variable chemotherapy use, and technical variations applied. In case of colorectal liver metastases (CRLM) in a 2-centers study including 33 patients, disease free survival (DFS) after TSH for CRLM was 85% and 68% at 1 and 2 years, respectively [52]. In a larger cohort [55] the rate of DFS of those patients, who completed the second stage (n=47), reached 39% at 1 year and 20% at 3 years in an intent-to-cure analysis but only in patients, who underwent both stages. In comparison, the 1- and 2-year DFS in the ALPPS registry for patients with CRLM of 59% and 41%, respectively, with a median DFS of 14 months, may be considered acceptable, particularly assessing that almost all patients could eventually benefit from a curative resection [80].

A study by Oldhafer et al. [63] found that 86% of patients had a tumor recurrence with a median time of 8 months after ALPPS. They stated that ALPPS had the same potential for tumor progression as PVE. Oldhafer also described distant metastases.

A possible hypothesis to explain this data is that the induction of liver hypertrophy due to release of growth factors which increase the chance of intrahepatic/extrahepatic metastases. In addition, immunosuppression due to the extensive surgical resection triggers growth and tumor spread.

Another concern raised was that liver is strongly manipulated in the ALPPS procedure, which may promote tumor cell dissemination by detaching cells into the systemic and pulmonary circulation. Additionally, the local and systemic release of growth factors may further stimulate tumor growth. A further evidence was presented by Fukami [81]; his group performed a biopsy of the same metastatic liver lesion during the first and second laparotomy by measuring an indicator of tumor glucose metabolism "Ki-67 index". They described a significant increase in the marker expression in the second biopsy of 80% compared to 60% initial values. Although the data is weak for the limited number of patients enrolled, may reflect the possible push towards a greater aggressiveness of the tumor induced by the procedure.

Recurrence rate data are unsatisfactory with ranges from 5 to 86% due to different follow-up periods and heterogeneous case evaluated [23].

The observation that DFS is lower in ALPPS than TSH could come to the conclusion that many patients go to the procedure with little or no oncological benefit. Numerous studies showed that in TSH the DFS are higher and morbidity lower than ALPPS [62,82,83].

Actual gold standard indication for ALPPS are colorectal bilobar liver metastases in patients younger than 60 years [80]. Pringle's manouvres , primitive liver disease, previously systemic chemo or radiotherapy, cholestasis, primary biliary tumors (Klatskin tumor's) are risk factors for a worse prognosis after first surgical procedure for a reduces liver regeneration. Although TSH and PVE should be preferred in oncological terms when it is possible with these techniques to achieve complete resection [17].

In conclusion, ALPPS should be seen an interesting evolution of two-stage procedures for colorectal liver metastases. Its advantage in terms of feasibility compared with TSH is real but limited when the procedures are clearly indicated. Additionally, ALPPS should be proposed to patients with caution and warnings about a still higher morbidity than with TSH or one stage hepatectomy, which will remain the standard approach for obtaining R0 resection in patients with bilobar advanced CRLM and inadequate FLR [84]. It is foreseeable that with the

rapid diffusion of new neoadjuvant chemotherapic regimens, the need for ALPPS, as a safe strategy to the classic two-stage approach, will increase. In fact more patients are and will gain resectability due to partial or sometimes full response to chemotherapy protocols. Thus a multidisciplinary approach starting with aggressive neoadjuvant regimen, under indications of institutional tumor boards, will push more patients to ALPPS. In the history of liver resection," ALPPS is like a newborn baby. It needs sufficient time to grow and mature" [23].

Conclusion

Nowadays the feasibility of major liver resections is well established and the coming years will lead to improve the safety of liver resections. In the spectrum of future surgical barriers, the risk of postoperative liver failure will always be the main concern in pushing the surgical indications on complicated patients. Taking into account the basic hepatic functional principles, the regeneration techniques now focused on pure quantitative hypertrophy will move in an attempt to achieve an higher qualitative hypertrophy. The progression of these procedures will have to keep in mind some fundamental factors: minimisation of morbidity and mortality associated with the given procedures. The rapid increase of FLR in order to prevent disease progression and further research should be carried out to clarify the causes leading to tumor progression during the period between the two procedures. In addition,

another issue that remains unresolved is to refine the role of chemotherapy and the optimal timing to use it.

In the end, the evolution of surgery in this field has led to encouraging success but surgeons should never forget that a justified non-operative approach will always be less invasive than the least invasive surgical approach [85].

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