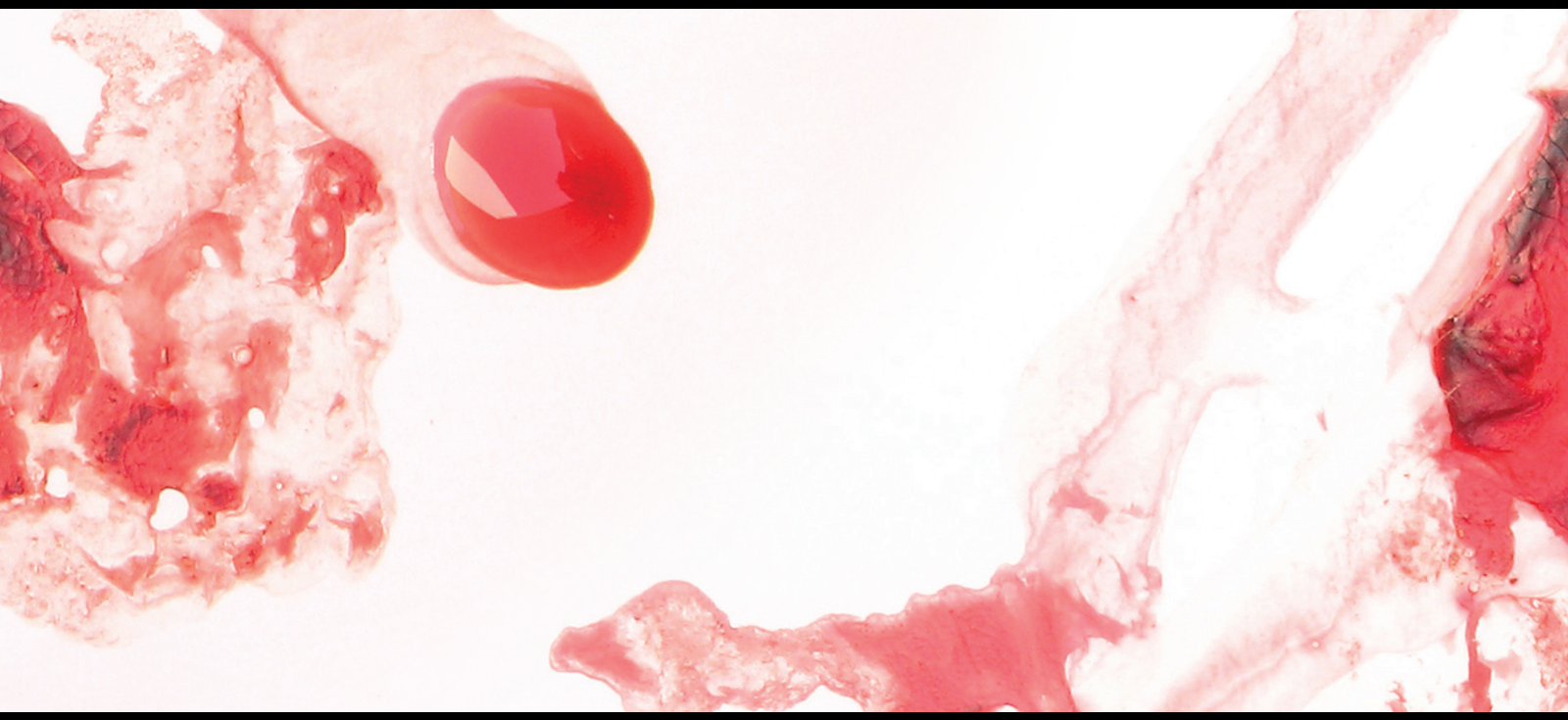
HPB Surgery

Innovative Strategies and Recent Advances in Liver Surgery

Guest Editors: Andrea Lauterio, Luciano De Carlis, Irinel Popescu, and Juan García-Valdecasas



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Editorial

Innovative Strategies and Recent Advances in Liver Surgery

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Techniques for hepatic surgery have evolved over the past few decades and have broadened indications for liver resection (LR) for liver tumors. New strategies including downsizing chemotherapy, two-stage LR with or without portal vein embolization, and resection combined with ablative methods allow tailoring the treatment to each patient depending on condition of the liver and tumor burden. In the recent years, the new dissector devices have been developed and together with the use of intraoperative ultrasound allow a new approach to the anatomical ultrasound-guided liver resection, even for large tumors located in challenging positions.

Improvements in imaging evaluation with high-resolution CT scan or MRI allow new methods for the study of the future remnant liver and play an important role in the planning of the resection strategy reducing the risk of major complications and liver failure, especially in patients who undergo major resection. In addition, development of new technology in local ablative therapies for liver tumors is posing a competition to LR.

The incidence of hepatocellular carcinoma (HCC) is climbing rapidly and in a current climate of organ shortage has led to the re-evaluation of locoregional therapies and resectional surgery to manage the case load. The introduction of biological therapies has had a new dimension to care, adding to the complexities of multidisciplinary team working in the management of HCC. S. E. Khorsandi and N. Heaton give a very comprehensive overview of the present day management strategies and decision making for patients with HCC.

Simultaneous resection of primary colorectal carcinoma (CRC) and synchronous liver metastases (SLM) is subject of debate with respect to morbidity in comparison to staged resection. In contrast to the extensive literature on staged laparoscopic colorectal and laparoscopic liver surgery, there are only a few reports on combined laparoscopic colorectal and liver resection.

L. T. Hoekstra and colleagues report their initial experience of simultaneous laparoscopic resection of primary CRC and SLM. According to the modern literature, the authors conclude that patient selection and expertise are essential for this complex type of surgery and the multidisciplinary team should decide on optimal timing within multimodality schedules.

I. Popescu and S. T. Alexandrescu challenge recent evidence in the different surgical options for initially unresectable colorectal liver metastases. The authors illustrate the available oncosurgical modalities including liver resection following portal vein ligation/embolization, "two-stage" liver resection, one-stage ultrasonically guided liver resection, hepatectomy following conversion chemotherapy, and liver resection combined with thermal ablation. The authors discuss the role of liver transplantation (LT) as a future opportunity in the treatment of unresectable CRLM in selected patients, taking into account the related ethical considerations especially in case of LT from living donor or LT with marginal grafts. Although the available data do not support liver transplantation as a routine procedure in patients with CRLM, this paper could promote the debate on this issue.

Partial liver transplantation, including split-liver and living donor liver transplantation, represents another important application of these advantages applied in the field of organ transplantation.

N. Akamatsu and Y. Sugawara provide a review article on the current trends and controversies in living donor liver transplantation (LDLT) for patients with HCV in relation to the perspectives from deceased donor.

They focused their attention on the recent advances in antiviral treatment for the recurrent hepatitis C after LT reporting the different strategies from the Japanese LDLT centers.

Minimally invasive approach in the field of HPB surgery is gaining popularity due to the availability of new laparoscopic instruments for liver transection. Laparoscopic LR has evolved significantly over the past decade moving from an experimental procedure to a standard part of the hepatic surgeon's armamentarium. Most recently, robotic-assisted technology offers solutions to overcome the limitations of conventional laparoscopic resection.

With the review paper titled *"Laparoscopy in liver transplantation: The future has arrived,"* Q. Lai and colleagues shed further light on the role of the laparoscopy in this field of surgery. Intent of the review is to underline the current role of diagnostic and therapeutic laparoscopy in patients waiting for LT, in the living donor LT and in LT recipients.

G. Dapri and colleagues report their initial experience with single-incision transumbilical laparoscopic liver resection (SITLLR) with a detailed technical paper and discuss the future of this approach in terms of indications, potential benefits, and limitations in comparison with multiport laparoscopic technique.

Single incision transumbilical laparoscopy represents the latest advance of the laparoscopic approach; however, its use in LR still remains limited to small reported series, and further evaluation is required to assess the potential advantages and the improvement in the patients outcome. As reported by the authors, at this point of the experience, several questions on SITLLR remain to be addressed, concerning the feasibility and mostly the reproducibility of this technique, the indications, selection criteria, limitations, effect on postoperative outcomes, and long-term results.

F. Romano et al. provide a summarizing paper illustrating methods to prevent bleeding in hepatic surgery. This is of particular interest, as bleeding in HPB surgery represents one of the most common features associated with poor outcome. The paper is based on the literature information and author's experience, and the aim of the study is to investigate the principal solutions to the problem of high blood loss in LR focusing on technological approach to the parenchyma transection.

The aim of this special issue is to update and promote interchange of the current knowledge and recent progress focusing on innovative strategies and recent advances in liver surgery. These manuscripts represent an exciting and insightful snapshot of the recent advances in liver surgery. State-of-the-art, existing challenges, and emerging future topics are highlighted in this special issue, which may inspire the reader and help advance in this field of surgery. We would like to thank all the authors and reviewers for making this special issue in HPB surgery possible.

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Review Article

Living-Donor Liver Transplantation and Hepatitis C

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Hepatitis-C-virus- (HCV-) related end-stage cirrhosis is the primary indication for liver transplantation in many countries. Unfortunately, however, HCV is not eliminated by transplantation and graft reinfection is universal, resulting in fibrosis, cirrhosis, and finally graft decompression. In areas with low deceased-donor organ availability like Japan, living-donor liver transplantation (LDLT) is similarly indicated for HCV cirrhosis as deceased-donor liver transplantation (DDLT) in Western countries and accepted as an established treatment for HCV-cirrhosis, and the results are equivalent to those of DDLT. To prevent graft failure due to recurrent hepatitis C, antiviral treatment with pegylated-interferon and ribavirin is currently considered the most promising regimen with a sustained viral response rate of around 30% to 35%, although the survival benefit of this regimen remains to be investigated. In contrast to DDLT, many Japanese LDLT centers have reported modified treatment regimens as best efforts to secure first graft, such as aggressive preemptive antiviral treatment, escalation of dosages, and elongation of treatment duration.

1. Introduction

Since the first successful application of living donor liver transplantation (LDLT) in 1990 [1] and subsequent successful LDLT for adult recipient in 1994 [2], the use of live donors for liver transplantation has been widely applied to adult recipients where the availability of deceased-donors is severely restricted, like in Japan [3], and also accepted as a solution to the cadaveric donor shortage in Western countries [4].

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in developed countries [5, 6], including Japan [7]. Unfortunately, liver transplantation does not cure HCV-infected recipients, but re-infection of HCV universally occurs and disease progression is accelerated compared with that in the nontransplant population, resulting in poor outcomes for HCV-infected recipients [8].

The aim of this paper was to overview the current trends and controversies in LDLT for patients with HCV in relation to the perspectives from deceased-donor liver transplantation (DDLT).

2. Natural History of Hepatitis C after Orthotopic Liver Transplantation

Accumulating perspectives of disease recurrence in HCV-infected recipients have been obtained in DDLT within the last two decades. HCV reinfection occurs just after reperfusion followed by a rapid increase in HCV ribonucleic acid (RNA) levels within 4 postoperative months [9]. The histologic features of liver injury usually resemble those of nontransplant HCV hepatitis typically developing after 3 months, but the clinical presentation, severity, and outcome are extremely heterogeneous and more profound compared to those in immune competent patients [10]. Progression to cirrhosis usually takes 9 to 12 years after liver transplantation with a linear progression of histologic fibrosis [10, 11]. A less common, but well-documented, form of

recurrence is called fibrosing cholestatic hepatitis (<10%), possibly mediated by a direct cytopathic mechanism under an extremely high viral load and immune-compromised condition. Graft failure occurs in 50% of recipients within a few months after fibrosing cholestatic hepatitis develops [12]. Some HCV-reinfected recipients, however, show no apparent disease progression for at least the first decade and their graft injury remains mild or even absent despite a high vira burden.

Overall, cirrhosis develops in approximately 25% of liver transplant recipients (range 8%–44%) after 5 to 10 years and this percentage is likely to increase with an increase in the follow-up period [10, 11]. Once cirrhosis is complete, survival time is severely decreased and decompression is encountered with cumulative rates at 1 and 3 years of 40% and 60%, respectively, which finally results in graft failure [11, 13].

The development of decompensated cirrhosis due to recurrent hepatitis C is now the most frequent cause of graft failure, patient death, and the need for retransplantation in HCV-infected recipients [11, 13–17]. As a result, survival is significantly decreased compared with other indications, an overall 10% difference at 3 years [18]. In the most recent United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) study from the United States, 3-year survival is 78% among 7459 HCV-positive recipients compared with 82% among 20734 HCV-negative recipients ($P < 0.0001$; http://www.unos.org) [19].

The poor outcome of HCV-positive recipients has resulted in the divergence in transplant outcomes between HCV-positive recipients and HCV-negative recipients. Improvements in organ preservation, surgical techniques, and postoperative care have dramatically improved the survival of HCV-negative recipients over the last two decades, whereas this has not been the case in HCV-positive recipients for whom outcome has remained unchanged or even worsened over time [19–22].

3. Current Status of LDLT

In areas with low deceased-donor organ availability like Japan, the indication of LDLT for HCV cirrhosis is similar to that of DDLT [7], whereas in Western countries, LDLT is conducted in an attempt to alleviate the shortage of donor organs and decrease the mortality among patients awaiting transplants, accounting for only 3% to 4% of all liver transplants [23].

According to the Japan Liver Transplantation Society [24], a total of 6097 LDLTs, comprising 98% of all liver transplants, have been performed till the end of 2010 in Japan. Among those, 3796 were adult cases including 1200 (32%) cases of HCV-related disease as a leading indication for adult LDLT. The 1, 3, 5, and 10 year survival rates of all adult LDLT and those of HCV-positive adults were 81%, 75%, 72%, and 66%, and 78%, 72%, 68%, and 59%, respectively, without difference.

In the United States, nearly 3000 LDLTs have been performed by the end of 2009, with decreased number of cases annually, comprising only 4.5% of all liver transplants [23, 25, 26].

4. LDLT as a Risk Factor for Recurrent Hepatitis C Studies Comparing Outcomes of LDLT and DDLT

Based on the significant negative impact of recurrent hepatitis C on recipients' outcome, it is critical to identify the factors related to severe recurrent hepatitis C [8, 13]. In the transplant setting, many factors contribute to disease progression compared with nontransplant patients [13], including, viral-related factors [10, 27–36], donor age [17, 37–43], recipient-related factors [32, 44–49], graft and surgical factors [40, 50–57], and immunosuppressive agents [58–75] (Table 1) however, many aspects remain unclear and require further investigation [8]. Among those, the possibility of increased severity of recurrent HCV in LDLT patients had been one of the hottest debates. The benefit of LDLT might be offset if the outcome of LDLT for HCV-positive recipients is worse than that of DDLT.

Early studies raised some negative concerns regarding the outcomes of LDLT in HCV patients, such as a poorer graft outcome and earlier and more aggressive HCV recurrence after LDLT compared with DDLT [144–146]. Several theories have been proposed to explain the differences in HCV recurrence between LDLT and DDLT recipients. One possible explanation is that the intense hepatocyte proliferation that occurs in partial liver grafts may lead to increased viral translation and replication [145, 147–149]. Genetic donor-recipient similarity is another proposed mechanism for more severe HCV recurrence [150, 151]. Recent studies, however, comparing outcomes of LDLT and DDLT in HCV-infected patients have not only failed to identify LDLT as a risk factor for more intense viral recurrence with impaired outcome, but also revealed improved results in LDLT recipients [39, 84–95], which do not support the aforementioned speculations. Alternatively, recent studies favored the theory that outcomes of LDLT for HCV cirrhosis could be better than those of DDLT due to the younger donor age and shorter ischemic time of LDLT grafts. The studies comparing outcomes between LDLT and DDLT in HCV-infected recipients are summarized in Table 2.

While several earlier studies demonstrated impaired patient/graft survival and severe histologic findings in LDLT [144–146], the majority of studies reported equal or even improved outcomes both in patient/graft survival and in fibrosis progression in LDLT [39, 84–95]. Since the large UNOS database study [87] demonstrated comparable short-term (24 months) survival between LDLT and DDLT, subsequent studies with considerable follow-up period have been published demonstrating comparable or even superior outcome in LDLT. Five-year patient survival ranged 71% to 84% in HCV-positive LDLT recipients among studies with sufficient follow-up period [39, 86, 94, 95]. Additionally, as Terrault et al. [92] reported, the learning curve for the LDLT procedure may have a considerable impact on the outcome of LDLT for HCV cirrhosis, which has been repeatedly pointed

Table 1: Factors associated with the severity of recurrent hepatitis C after liver transplantation.

Variables	Effect on recurrent hepatitis C
Donor and graft factors	
Age [17, 37–43]	More severe disease (>40, >50, >65)
Steatosis [56, 57, 76–79]	Few studies
Prolonged ischemic time [54, 55, 80–83]	More severe disease
HCV+ graft [6, 22, 40, 50–53, 76]	No influence
Reduced size versus whole liver (LDLT versus DDLT) [39, 84–95]	No difference
Pretransplant recipient factors	
Genotype 1b [8, 32, 33, 35, 40]	Controversial
Pre-LT higher viral load [21, 28, 96, 97]	Unclear
Age [32, 44, 98]	Few studies
Race [45, 46, 99]	Few studies
Sex [20, 47, 48]	Few studies
HIV coinfection [100–107]	No influence
IL-28B gene polymorphism [49, 108–111]	More severe disease in CT and TT genotype
Posttransplant recipient factors	
Post-LT higher viral load [10, 27–31]	More severe disease
CMV infection [22, 29, 32, 112–116]	Unclear
Diabetes mellitus (Metabolic syndrome) [29, 117–121]	More severe disease
Immunosuppression	
Steroid bolus/OKT3 [6, 21, 22, 58, 59, 122–124]	More severe disease
Maintenance steroid [34, 60–62, 122]	Severe disease when rapidly tapered
Steroid free regimen [63–68, 125–127]	No influence
Tacrolimus versus cyclosporine [69–75]	No difference
Anti-IL-2 receptor antibodies [63, 126, 128–131]	Controversial
Azathioprine/mycophenolate mofetil [132–140]	Controversial
mTOR inhibitors [141–143]	Few studies

CMV: cytomegalovirus; DDLT: deceased-donor liver transplantation; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LDLT: living-donor liver transplantation; LT: liver transplantation; mTOR: mammalian target of rapamycin.

out by recent authors. Actually, none of reports after 2005 has found impaired outcome in LDLT.

These data should be interpreted with caution, however, because of the important clinical distinction between LDLT and DDLT. At the time of transplantation, DDLT recipients are far sicker than LDLT recipients as represented by a significantly higher MELD score, donor age is higher, and graft ischemic time is longer. Indeed, significantly poorer preoperative condition and older donor age in DDLT recipients were indicated in 7 and 6 studies, respectively, among 16 studies listed in Table 2. Additionally, cold ischemia time is significantly longer in DDLT than that in LDLT in all studies. All these factors, as presented in Table 1, are considered independent prognostic factors for severe HCV recurrence and impaired patient/graft outcome. Actually, Jain et al. [95], who recently reported that both patient/graft survival and histologic findings are better in LDLT, found in a subanalysis of the study that adjusting for MELD score (<25) and donor age (<50) resulted in similar outcomes.

Based on accumulating reports demonstrating comparable outcome of LDLT and DDLT for HCV cirrhosis, and refinement of surgical techniques and management in LDLT, hepatitis C recurrence by itself does not seem to explain the differences in patient/graft survival between LDLT and DDLT, and even improved outcomes could be achieved in LDLT due to the better quality of the graft, younger donors, and less sick recipient condition at the time of transplantation. Furthermore, based on these benefits of LDLT, donor selection to improve outcome of LDLT for HCV positive recipients could be assumed. Selecting younger donors [17] or donors with favorable IL-28B genotype [108, 109] could be possible future issues; however, with the severe lack of live donors, it seems impractical in clinical setting at present. Anyway, LDLT could be strongly recommended for HCV-positive patients whenever it is available.

5. Antiviral Treatment

Antiviral treatments for recurrent hepatitis C after liver transplantation include eradication of the HCV virus before transplantation with the use of pretransplant antiviral treatment, eradication of HCV virus early after transplantation preemptively to prevent graft damage, and treatment for established recurrent hepatitis C in the acute, or more commonly, chronic phase. Regardless of the antiviral treatment timing, interferon (INF), especially pegylated-INF (PEG-INF), in conjunction with ribavirin (RBV), is currently accepted as a standard key drug in achieving high sustained

Table 2: Studies comparing living-donor liver transplantation and deceased-donor liver transplantation in patients with hepatitis C cirrhosis.

Author	Year	*n* (LDLT/DDLT)	MELD score (LDLT/DDLT)	Donor age (LDLT/DDLT)	Cold ischemia time (h) (LDL/DDLT)	Follow-up (mo)	Histologic progression	Patient survival LDLT/DDLT (%)	Graft survival LDLT/DDLT (%)	Comments
Gaglio et al. [144]	2003	68 (23/45)	12.6/28*	NA	NA	24	NA	87/89	87/85	No difference in outcomes, increased risk of cholestatic hepatitis in LDLT
Garcia-Retortillo et al. [145]	2004	117 (22/95)	11 (5–24)/11 (2–28)	31 (19–58)/47 (13–86)#	NA	22	Significantly severe in LDLT	NA	NA	Severe hepatitis C recurrence in LDLT
Thuluvath and Yoo [146]	2004	619 (207/412)	NA	35.8 ± 0.4/38.9 ± 18.1#	3.9 ± 7.3/8.4 ± 4.5†	24	NA	79/81	74/73	Lower graft survival in LDLT
Humar et al. [85]	2005	51 (12/39)	17 (14–27)/24 (17–40)*	37.7 ± 9.2/42.8 ± 16.2#	10.2 ± 4.2/<1†	28.3	Significantly severe in DDLT	92/90	NA	LDLT may be at a low risk for HCV recurrence
Shiffman et al. [84]	2004	76 (23/53)	13.5 ± 1.1/16.2 ± 1.0	47.6 ± 2/47.8 ± 0.8	NA	36	No difference	79/82	76/82	No difference in outcomes
Maluf et al. [86]	2005	126 (29/97)	13.2 ± 1.1/21 ± 0.8*	NA	0.6 ± 0.2/7.5 ± 2.8†	72	NA	67/70	64/69	No difference in survival, more rejection in DDLT and biliary complications in LDLT
Russo et al. [87]	2004	4234 (279/3955)	NA (TB, PT and Cre were significantly worse in DDLT)	37/40#	8.1/2.6†	24	NA	83/81	72/75	No difference in outcomes
Bozorgzadeh et al. [88]	2004	100 (35/65)	14.9 ± 4/15.9 ± 5.3	34.6 ± 9.7/49.2 ± 20.4	NA	39	No difference	89/75	83/64	No difference in outcomes
Van Vlierberghe et al. [89]	2004	43 (17/26)	15 ± 9/15 ± 8	31 ± 8/48 ± 17	3.1 ± 1.3/11.1 ± 2.6†	12	No difference	No difference (Presented with only figure)	No difference (Presented with only figure)	No difference in outcomes in short-term
Schiano et al. [90]	2005	26 (11/15)	14 (9–19)/18 (10–31) $P = 0.05$	33 (20–54)/47 (13–73)	0.6 (0.3–1.0)/10 (4.4–20)†	24	NA	73/80	73/80	No difference in survival, accelerated viral load increase in LDLT
Guo et al. [91]	2006	67 (15/52)	16.9 ± 6.9/19.0 ± 8.3	NA	NA	24	No difference	93/96	87/94	No difference in outcomes
Terrault et al. [92]	2007	275 (181/94)	14 (6–40)/18 (7–40)*	38 (19–57)/41 (9–72)	0.8 (0.1–8)/6.7 (0.2–10)†	36	No difference	74/82	68/80	No significant difference in patient/graft survival in experienced LDLT centers
Schmeding et al. [93]	2007	289 (20/269)	NA	38.6 ± 15.2/44.2 ± 12	NA	60	No difference	Better in DDLT ($P = 0.011$)	Better in DDLT ($P = 0.006$)	LDLT does not increase the risk and severity of HCV recurrence. No difference in patient/graft survival when HCC beyond Milan excluded.
Selzner et al. [94]	2008	201 (46/155)	14 (7–39)/17 (6–40)	38 (19–59)/46 (11–79)#	1.5 (0.5–4.9)/7.5 (1.1–16)†	60	Significantly severe in DDLT	84/78	76/74	Donor age, rather than transplant approach, affects the progression of HCV
Gallegos-Orozco et al. [39]	2009	200 (32/168)	14.6 ± 4.7/25.5 ± 5.9*	35 ± 12/40 ± 16 $P = 0.05$	NA	60	No difference	81/81	NA	LDLT is a good option for HCV cirrhosis
Jain et al. [95]	2011	100 (35/65)	14.5 ± 3.9/16.8 ± 7.3*	34.3 ± 9.3/47.2 ± 19.8#	11 ± 3.1 in DDLT	84	Significantly severe in DDLT at all time points	77/65	71/46	Both patient/graft survival and histologic findings were better in LDLT

*MELD score is significantly higher in DDLT.
#Donor age is significantly higher in DDLT.
†Cold ischemia time is significantly longer in DDLT.
Cre: creatinine; DDLT: deceased-donor liver transplantation; LDLT: living-donor liver transplantation; MELD: model for end-stage liver disease; NA: not available; PT: prothombin-time; TB: total bilirubin.

viral response (SVR) rate according to the perspectives obtained in nontransplant populations.

Former two strategies, however, have almost been abandoned in Western countries. Pretransplant treatment is severely limited by poor liver function, a high prevalence of nonresponders, severe cytopenia, and complications, including life-threatening infections [152], and to date, only six studies [153–158] have been published in this phase with differences in the treatment duration (6–14 months versus 2-3 months) and in regimens used (INF only, INF/RBV, or PEG-INF/RBV). Regardless of the approach used, the results are similar, resulting in the prevention of HCV re-infection in about 20% of treated patients with high discontinuation rate and high dose reduction rate [152]. Considering the less severe disease of LDLT recipients as discussed earlier, pretransplant antiviral treatment seems more preferable for LDLT recipients to improve outcome; however, no such trial has been published so far in LDLT setting. This issue also seems remain to be investigated in future studies as with the case in live donor selection issues.

Prophylactic or preemptive antiviral treatment generally means antiviral treatment with INF/PEG-INF and RBV started early posttransplant, without requiring evidence of recurrent hepatitis C. In published studies [159–164] of preemptive antiviral therapy, SVR rates are reported to range from 8% to 34% (5% to 43% for genotype 1 and 14% to 100% for genotypes 2 or 3), with the rates of dose reduction and drug discontinuation are approximately 70% and 30%, respectively, due to the existence of cytopenia, renal dysfunction, rejection, or extrahepatic complications, and high levels of immunosuppression in this time window. The most recently published prospective, multicenter, randomized study (PHOENIX study) by Bzowej et al. [165] was designed to compare the efficacy, tolerability, and safety of an escalating dose regimen of PEG-INF alpha 2a/RBV for 48 weeks for preemptive antiviral treatment versus no treatment, which showed only 22% SVR in the prophylaxis patients with the rate of marked HCV recurrence at 120 weeks (62% in prophylaxis patients versus 65% in observation patients), and comparable fibrosis progression 120 weeks as well as similar patient/graft survival in both study arms. Dose reduction and discontinuation were required in 70% and 28%, respectively. Based on these results, European and United States transplant societies do not support the routine use of preemptive antiviral therapy.

Consequently, initiating antiviral therapy with PEG-INF/RBV after the confirmation of recurrent hepatitis C in the graft by liver biopsies is the mainstay for the treatment of recurrent disease in Western countries [35, 166–190]. Most of the data come from uncontrolled studies with different designs regarding time to start treatment, regimen used, and follow-up, but treatment duration is generally 48 to 52 weeks. Therefore, the results were also very different, with SVR rates ranging 0% to 56% (median: 33%), discontinuation rates ranging 4% to 58%, and dose reduction rate ranging 28% to 100%. In addition, the survival benefit of the treatment has not been confirmed in most studies so far, and it is compelling to conclude that there is currently no evidence to support the antiviral treatment for recurrent graft hepatitis C due to the lack of clinical benefit and frequent adverse effects, as concluded by the recent Cochrane meta-analysis [191]. On the other hand, recent retrospective cohort studies with a considerable follow-up duration found improved patient/graft survival in patients who obtained an SVR after antiviral treatment [35, 192–194]. Further randomized clinical trials with appropriate trial methodology and adequate follow-up duration are necessary to confirm an actual survival benefit of antiviral treatment.

6. Reports from Japanese LDLT Centers

Although retransplantation is the only potentially curative option for those with decompressed cirrhosis due to recurrent hepatitis C, in contrast to Western countries where re-DDLT is spared as a last resort [195, 196], it is extremely unlikely in Japan to perform retransplantation for patients with recurrent end-stage hepatitis C, if not absolutely impossible. These backgrounds might have led to various modified strategies for the treatment of recurrent disease as best efforts to secure first graft, such as aggressive preemptive antiviral treatment, escalation of dosages, and elongation of treatment duration.

We have reported preemptive INF/RBV treatment for HCV-positive LDLT recipients [161, 197–199]. Preemptive treatment was started just after recipient's condition had become stable (approximately one month after LDLT) with low-dose INF alpha 2b and RBV (400 mg/day) followed by escalation to PEG-INF (1.5 μg/kg per week) and RBV (800 mg/day) depending on patient's tolerance. The treatment duration was not settled, and was continued for additional 12 months after the serum HCV-RNA became negative. The response was considered to be SVR provided negative serologic results for another 6 months after discontinuation of therapy. That is, nonstopping peg-INF/RBV approach was applied for non-responders. Among 122 HCV-positive LDLT recipients, 42 (34%) achieved SVR and those with SVR showed significantly improved survival when compared to those without SVR (cumulative 5-year survival rate; 97% versus 66%) [199].

Kyoto group also reported modified PEG-INF/RBV treatment with individualized extension, while they started antiviral treatment for cases with biopsy-proven recurrent disease [200–202]. They started with PEG-INF (1.5 μg/kg per week) and RBV (400–800 mg/day) for 12 months for all patients with recurrent hepatitis. Then, full dose treatment was continued for additional 8–22 months for those whose serum HCV-RNA became negative within 12 months, while patients who did not become negative for serum HCV RNA within 12 months continued to receive a low-dose PEG-INF (0.5–0.75 μg/kg per week) with or without reduced RBV (200 mg/day) as maintenance treatment. Among 80 patients with recurrent hepatitis C after LDLT, SVR was achieved in 31 (39%), while remaining 49 (61%) received maintenance therapy among those 26 (53%) discontinued. In comparison to fibrosis progression, no difference was observed between SVR group and maintenance treatment group with improved or stable fibrosis in both groups, while those who withdrew

from maintenance showed significantly deteriorated fibrosis [202].

Kyushu group performed antiviral treatment for 80 patients among 106 consecutive HCV-positive recipients, excluding 26 cases of early death, negative HCV RNA, and refusal for treatment [203]. Basically, they started with PEG-INF (0.5 μg/kg per week) and RBV (200 mg/day), then escalated to PEG-INF (1.5 μg/kg per week) and RBV (800 mg/day), with the treatment duration of 48 weeks and over 72 weeks for those with early viral response and for those without it, respectively. They reported overall SVR rate of 35%. They found both significantly severe fibrosis and impaired graft survival in those who did not show viral nor biochemical response.

Other Japanese centers [204–207] have also reported similar modified antiviral treatment with PEG-INF and RBV including dose escalation, treatment for all HCV-positive cases, and extension of treatment. Additionally, simultaneous splenectomy during LDLT operation in an attempt to improve tolerance to antiviral treatment, SVR rate and further graft survival should be noticed [198, 208, 209].

7. Conclusion

Hepatitis C is here to stay and will remain the most common indication for liver transplantation. In the areas where cadaveric organs are extremely limited like in Japan, indication of LDLT is same as that of DDLT, and recent studies have proved that LDLT can be performed as safely and effectively as DDLT for HCV-infected patients in experienced centers. Further investigation for more effective and tolerable antiviral treatment is warranted to secure the first live donor graft to the possible extent.

Abbreviations

DDLT:	Deceased-donor liver transplantation
HCV:	Hepatitis C virus
HIV:	Human immunodeficiency virus
INF:	Interferon
LDLT:	Living-donor liver transplantation
MELD:	Model for end-stage liver disease
MMF:	Mycophenolate mofetil
mTOR:	Mammalian target of rapamycin
PEG-INF:	Pegylated-interferon
RBV:	Ribavirin
RNA:	Ribonucleic acid
SVR:	Sustained viral response
UNOS/OPTN:	The United Network for Organ Sharing/Organ Procurement and Transplantation Network.

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Review Article

Bleeding in Hepatic Surgery: Sorting through Methods to Prevent It

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Liver resections are demanding operations which can have life threatening complications although they are performed by experienced liver surgeons. The parameter "Blood Loss" has a central role in liver surgery, and different strategies to minimize it are a key to improve results. Moreover, recently, new technologies are applied in the field of liver surgery, having one goal: safer and easier liver operations. The aim of this paper is to review the different principal solutions to the problem of blood loss in hepatic surgery, focusing on technical aspects of new devices.

1. Introduction

Liver resection is considered the treatment of choice for liver tumours. Despite standardized techniques and technological advancing for liver resections, an intraoperative haemorrhage rate ranging from 700 to 1200 mL is reported with a postoperative morbidity rate ranging from 23% to 46% and a surgical death rate ranging from 4% to 5% [1–6].

The parameter "*Blood loss*" has a central role in liver surgery and different strategies to minimize it are a key to improve these results. Bleeding has to be considered a major concern for the hepatic surgeon because of several reasons. At first, it is certainly the major intraoperative surgical complication and cause of death and historically one of the major postoperative complication together with bile leaks and hepatic failure [5–9].

Besides, a high intraoperative blood loss is associated with a higher rate of postoperative complication and shorter long-term survival [10–13]. Furthermore, it is associated with an extensive use of vessel occlusion techniques, directly correlated with higher risk of postoperative hepatic failure. Last, a higher value of intraoperative blood loss is associated with a higher rate of perioperative transfusions; and host immunosuppression associated with transfusions with a dose-related relationship is correlated with a higher rate of complication (in particular infections) and recurrence of malignancies in neoplastic patients [11, 12, 14–21]. In order to reduce transfusions, hepatic surgeon has also not to misinterpret postoperative fluctuations of blood parameter: Torzilli et al. demonstrated that haemoglobin rate and haematocrit after liver resection show a steady and significant decrease until the third postoperative day and then an increase, so this situation has to be explained as physiological and does not justifies blood administration [22].

2. How Can We Reduce Bleeding in Live Surgery?

This study is based on the literature information and our own experience.

The aim of the study is to investigate the principal solutions to the problem of high blood loss in hepatic resection.

2.1. The Role of the Surgeon. Most blood loss during liver resection occurs during parenchymal transection. Hepatic surgeon has different ways to control bleeding.

2.1.1. Vessel Occlusion Techniques. Those techniques are based on the idea that to limit the blood flow through the liver during parenchymal transection can reduce the haemorrhage. Although various forms and modified techniques of vascular control have been practiced, there are basically two main strategies; inflow vascular occlusion and total vascular exclusion [23, 24]. Inflow vascular occlusions are techniques that limit anterograde blood flow with the clamping of all the triad of the hepato-duodenal ligament (*Pringle's manoeuvre*), only of the vascular pedicles (selective clamping of the portal vein and the hepatic artery or *bismuth technique*) or *intravascular portal clamping*. During Pringle's maneuvre, the hepatoduodenal ligament is encircled with a tape, and then a vascular clamp or tourniquet is applied until the pulse in the hepatic artery disappears distally. The PM has relatively little general haemodynamic effect and no specific anaesthetic management is required. However, bleeding can still occur from the backflow from the hepatic veins and from the liver transection plane during unclamping. The other concern is the ischaemic-reperfusion injury to the liver parenchyma, especially in patients with underlying liver diseases [25]. The continuous Pringle manoeuvre (CPM) can be safely applied to the normal liver under normothermic conditions for up to 60 minutes and up to 30 minutes in pathological (fatty or cirrhotic) livers, although much longer durations of continuous clamping 127 minutes in normal livers and 100 minutes in pathological livers have been reported to be safe [26, 27]. One way to extend the duration of clamping and to reduce ischaemia to the remnant liver is by the intermittent Pringle manoeuvre (IPM). It involves periods of inflow clamping that last for 15–20 minutes followed by periods of unclamping for five minutes (mode 15/5 or 20/5), or five minutes clamping followed by one minute unclamping (mode 5/1) [28, 29]. IPM permits a doubling of the ischaemia time, when compared with CPM, and the total clamping time can be extended to 120 minutes in normal livers and 60 minutes in pathological livers. The disadvantage of IPM is that bleeding occurs from the liver transaction surface during the unclamping period and, thus, the overall transection time is prolonged as more time is spent in achieving haemostasis. Belghiti et al. [28] revealed that there was no significant difference in total blood loss or volume of blood transfusion between CPM and IPM (mode 15/5). However, they noticed that pathological livers tolerated CPM poorly.

A newer perspective on inflow occlusion comes from the concept of ischaemic preconditioning (IP). It refers to an endogenous self-protective mechanism by which a short period of ischaemia followed by a brief period of reperfusion produces a state of protection against subsequent sustained ischaemia-reperfusion injury [30, 31]. The IP is performed with ten minutes of ischaemia followed by ten minutes of reperfusion before liver transaction with CPM [32]. Hemihepatic clamping (half-Pringle manoeuvre) interrupts the arterial and portal inflow selectively to the right or left liver lobe that is to be resected [33, 34]. It can be performed with or without prior hilar dissection. It can also be combined with simultaneous occlusion of the ipsilateral major hepatic vein. The advantage of this technique is that it avoids ischaemia in the remnant liver, avoids splanchnic congestion, and allows clear demarcation of the resection margin. The disadvantage is that bleeding from the parenchymal cut surface can occur from the nonoccluded liver lobe.

Segmental vascular clamping entails the occlusion of the ipsilateral hepatic artery branch and balloon occlusion of the portal branch of a particular segment. The portal branch is identified by intraoperative ultrasound and puncture with a cholangiography needle through which a guide wire and balloon catheter are passed [35, 36].

Total vascular exclusion (TVE) combines total inflow and outflow vascular occlusion of the liver, isolating it completely from the systemic circulation. It is done with complete mobilisation of the liver, encircling of the suprahepatic and infrahepatic IVC, application of the Pringle manoeuvre, and then clamping the infrahepatic IVC followed by clamping of the suprahepatic IVC. TVE is associated with significant haemodynamic changes and warrants close invasive and anaesthetic monitoring. Occlusion of the IVC leads to marked reduction of venous return and cardiac output, with a compensatory 80% increase in systemic vascular resistance and 50% increase in heart rate and, thus, not every patient can tolerate it. TVE can be applied to a normal liver for up to 60 minutes and for 30 minutes in a diseased liver. The ischaemic time can be extended when combined with hypothermic perfusion of the liver [37, 38]. Apart from the unpredictable haemodynamic intolerance, postoperative abdominal collections or abscesses and pulmonary complications are more common in TVE, when compared with CPM.

Inflow occlusion with extraparenchymal control of hepatic veins is a modified way of performing TVE. The main and any accessory right hepatic vein, the common trunk of the middle and left hepatic veins, or the separate trunks of the middle and left hepatic veins (15% of cases) are first dissected-free and looped. It has been reported that the trunks of the major hepatic veins can be safely looped in 90% of patients [39, 40]. The loops can then be tightened or the vessels can be clamped after inflow occlusion is applied, so that the liver lobe is isolated from the systemic circulation without interrupting the caval flow. It can be applied in a continuous or intermittent manner. The maximal ischaemia time is up to 58 minutes under continuous occlusion. This technique is more demanding than TVE, but it can avoid the haemodynamic drawbacks of TVE while at the same time provide almost a bloodless field for liver transection.

2.1.2. Instruments and Technique for Resections. Although a large part of improvements of these last decades in liver surgery can be correlated to a better knowledge of the surgical hepatic anatomy (Couinaud's segmentation of liver [41]), better monitoring during anaesthesia, and

introduction of intraoperative ultrasonography and of other imaging techniques, the choice of surgical technique for sectioning the liver has surely important repercussions on the intervention's outcome.

There are two techniques we could define traditionally: the *finger fracture method* and the *clamp crushing method*. These are the oldest techniques for hepatic transection and are still employed especially by long-experienced surgeons. The use of traditional techniques to isolate bile ducts and vascular pedicles from the surrounding parenchyma provides for employment of clips or sutures for sealing bile ducts and vascular vessels and for other haemostasis techniques to stop haemorrhage from the resection's surface. There are several studies that sustain that traditional methods are still competitive with a new technique based on utilization of special devices [1, 42, 43].

Introduction of new devices for liver dissection surely have an important role, in particular for reduction of intraoperative blood loss. Actually the most important devices useful for liver resection are presented a technical point of view and analysed to find the advantages (A) and the disadvantages (D) correlated to their employment.

Harmonic Scalpel, HS (Johnson and Johnson Medical, Ethicon, Cincinnati, OH, USA), also known as "Ultrasonically Activated Scalpel" or "Ultrasonic Coagulation Shears," this instrument was introduced in the early 1990s. The ultrasound scissors system includes a generator with a foot switch, the reusable handle for the scalpel, and the cutting device with scissors. The scissors are composed by a moveable blade and by a fixed longitudinal blade that vibrates with an ultrasonic frequency of 55,5 kHz (55.500 vibrations per second). HS can simultaneously cut and coagulate causing protein denaturation by destroying the hydrogen bonds in proteins and by generation of heat in vibrating tissue. This generated heat denatures proteins and forms a sticky coagulum that covers the edges of dissection. Although the heat produces no smoke and thermal injury is limited, the depth of marginal necrosis is greater than that incurred by either the water jet or CUSA. The lateral spread of the energy is 500 micrometers.

A: HS is the only instrument that can simultaneously cut and coagulate (it can coagulate vessel until 2-3 mm of diameter [44]); it is useful on cirrhotic liver [45]; no electricity passes through the patient and there is no smoke production (especially useful in laparoscopic surgery); it can be used in laparoscopic and laparotomic surgery. D: the instrument results in a continuous bleeding risk related to the blind tissue penetration to coagulate vessels hidden into the hepatic parenchyma. Studies demonstrate that HS is not capable of reducing blood loss and operating time compared to traditional techniques [46, 47], cannot coagulate vessel over 2-3 mm of diameter which have to be clipped, and is legated or sealed with other instruments; HS is not easy to use as a blunt dissector and has substantially demonstrated its usefulness only during the resection of the superficial part of liver (2-3 cm) free from large vessels and bile ducts; besides some studies have demonstrated that HS increases the rate of postoperative bile leaks [48, 49], raising the concern that HS may not be effective in sealing bile ducts. The use of HS in liver cirrhosis is controversial. The greatest concern with the use of the harmonic scalpel is the risk of shearing [50]. Slight errors of movement can shear parenchyma without completely coagulating vessels and/or ducts. Moreover, it is expensive (the generator costs US$20.000 and the handle US$250).

2.1.3. Cavitron Ultrasonic Surgical Aspirator, CUSA (Valleylab). The use in liver surgery of this instrument, also known as ultrasonic dissector, was described for the first time in the literature in 1979 by Hodgson [51]. CUSA is a surgical system in which a pencil-grip surgical hand piece contains a transducer that oscillates longitudinally at 23 kHz and to which a hollow conical titanium tip is attached. The vibrating tip of the instrument causes explosion of cells with a high water content (just like hepatocytes) and fragmentation of parenchyma sparing blood and bile vessel because of their walls prevalently composed by connective cells poor of water but rich of intracellular bonds. The device is equipped by a saline solution irrigation system that cools the hand piece and washes the transection plane and by a constant suction system that removes fragmented bits of tissue and permits excellent visualization. A: CUSA is capable of dissecting, offering excellent visualization useful in particular during nonanatomical resections and approaching the deeper portion of the transaction plane [52, 53]. (1) The instrument allows surgeons to see clearly blood and biliary vessels as they dissect through the liver [54], (2) use of the instrument allows them to avoid prolonged extrahepatic vascular control, and (3) the operation actually takes less time because the vessels are continuously controlled during the dissection and there is little need for a prolonged search for bleeding or biliary vessels after the specimen has been removed.

A previous retrospective study from Fan showed that the ultrasonic dissector resulted in lower blood loss, lower morbidity, and lower mortality compared with the clamp crushing technique [55]. Furthermore, ultrasonic dissection resulted in a wider tumor-free margin because of a more precise transection plane.

D: CUSA cannot coagulate or realize haemostasis and even if some studies sustain it to be capable of reducing intraoperative blood loss, operating time, and duration of vessel occlusion [56], important studies demonstrate that CUSA cannot offer these advantages if compared with traditional techniques; a prospective trial by Rau et al. showed no statistical difference in the reduction of blood loss with the use of CUSA as compared to conventional methods [57]; another trial by Takayama et al. [53], in fact, noted a greater median blood loss. CUSA causes more frequent tumour exposure at the surgical margin than traditional techniques [1] and it is less useful for cirrhotic livers because the associated fibrosis prevents easy removal of hepatocytes [58]; besides, some authors found using CUSA method (compared to clamp crushing method) an increase of venous air embolism without evidence of hemodynamic compromise but with increased risk of paradoxical embolism in cirrhotic patients [59]. Moreover, CUSA should be used in association

with other devices which are able to perform hemostasis. The instrument seems cumbersome and complicated to inexperienced operating room personnel. Therefore, it is easy for the instrument to malfunction. The fact that the instrument works by removing a margin of liver tissue makes it, by nature, less attractive for harvesting liver for living-donor transplantation.

2.1.4. Tissuelink Monopolar Floating Ball, TMFB (Floating Ball, TissueLink Medical, Dover, NH, USA). This new instrument was put on the market in 2002 and it is a linear device that employs radiofrequency (RF) energy focused at the tip to coagulate target tissue. The tip is provided with a low volume (4–6 mL/min) saline solution irrigation that makes easier the conduction of RF in surrounding tissue and cools the tip itself avoiding formation of chars. TMFB can seal vascular and bile structures up to 3 mm in diameter by collagen fusion. These qualities make this device an excellent instrument for achieving haemostasis and in particular for precoagulating (with a painting movement) parenchyma and vessels prior to transection, preventing blood loss.

Otherwise, continuously heating tissue underneath a cool layer, however, causes a buildup of steam that can result in tissue destruction. The latter phenomenon is known as steam popping [60].

There are two models on the market, the DS3.0 with blunt tip that simply coagulates and the DS3.5-C Dissecting Sealer that is provided with sharp tip that can also dissect. A: the instrument is, in a sense, "friendlier" to most surgeons. In other words, surgeons, who are usually adept at using cautery, can easily understand this mechanism of action and use it accordingly. TMFB can coagulate (and the Dissecting Sealer can also cut) tissues and seals blood and bile ducts up to 3 mm in diameter, is able to reduce blood loss and the recourse to vessel occlusion techniques if compared to traditional techniques [61–63], offers good results also in cirrhotic livers and cystopericystectomy [64], and has a saline irrigation that avoids production of smoke, chars, and sticky coagulum to which the device could stick causing new bleeding when it is moved away. TMFB, used on the cut liver surface after dissection, destroys eventual additional cancer cells at the margin of resection; in order to assure sterile margins, extra tissue destruction at the margins of resection may be desirable for tumor excisions. Otherwise, this could be a disadvantage in case of living-donor liver transplantation. It is available for both laparotomic and laparoscopic surgery and it is quite cheap and compatible with most electrosurgical generator currently available.

D: TMFB is not able to coagulate vessel over 2-3 mm of diameter which has to be clipped, legated, or sealed with other instruments [65]. Moreover, studies do not demonstrate its efficacy to reduce operating time if compared with traditional techniques [66].

2.1.5. The Aquamantys System. The Aquamantys System employs transcollation technology to simultaneously deliver RF (radiofrequency) energy and saline for haemostatic sealing and coagulation of soft tissue and bone at the surgical site. Transcollation technology is used in a wide variety of surgical procedures, including orthopaedic joint replacement, spinal surgery, orthopaedic trauma, and surgical oncology. Transcollation technology simultaneously integrates RF (radiofrequency) energy and saline to deliver controlled thermal energy to the tissue. This allows the tissue temperature to stay at or below 100°C, the boiling point of water. Unlike conventional electrosurgical devices which operate at high temperatures, transcollation technology does not result in smoke or char formation when put in contact with tissue. Blood vessels contain Type I and Type III collagen within their walls. Heating these collagen fibers causes radial compression, resulting in a decrease in vessel lumen diameter. Using the Aquamantys generator with patented bipolar and monopolar sealers, surgeons can achieve broad tissue-surface haemostasis by applying transcollation technology in a painting motion, or it can be used to spot-treat bleeding vessels. This is capable of sealing structures 3–6 mm in diameter without producing high temperature or excessive charring and eschar. Structures more than 6 mm in diameter should be divided in conventional manner with clips or ties. Constant suction is required to clear the saline used for irrigation.

A: its use is "friendlier" to most surgeons, easy to learn most surgeons are comfortable after 5-6 procedures. It seals blood and bile ducts up to 6 mm in diameter and is able to reduce blood loss and the recourse to vessel occlusion techniques. Moreover, it offers good results also in cirrhotic livers [67] and destroys eventual additional cancer cells at the margin of resection.

D: it is expensive and pace of liver transaction could be low.

2.1.6. Bipolar Vessel Sealing Device, BVSD (LigaSure, Valleylab Inc., Boulder, CO, USA). The use in liver surgery of this instrument was described for the first time in the literature in 2001 by Horgan [68]. The LigaSure System includes a generator with a foot switch and a clamp-form hand piece that can be used for parenchymal fragmentation and isolation of blood and bile structures just like in clamp crushing technique before application of energy; it employs RF to realize permanent occlusion of vessels or tissue bundle. The LigaSure generator has a Valleylab's Instant Response technology, a feedback-controlled response system that diagnoses the tissue type in the instrument jaws and delivers the appropriate amount of energy to effectively seal the vessel: when the seal cycle is complete, a generator tone is sound, and the output to the handset is automatically discontinued. BVSD is capable of obliterating the lumen of veins and arteries up to 7 mm in diameter by the fusion of elastin and collagen proteins of the vessel walls and that makes BVSB the only safe and real alternative to sutures and clips for sealing vessel [69–71].

A: BVSD coagulates sealing vessels up to 7 mm in diameter with minimal charring, thermal spread, or smoke; it is capable of reducing blood loss and the recourse to vessel occlusion techniques if compared to traditional techniques [8, 72, 73]. A recently published randomized controlled

trial demonstrated that the use of LigaSure in combination with a clamp crushing technique resulted in lower blood loss and faster transaction speed in minor liver resections compared with the conventional technique of electric cautery or ligature for controlling vessels in the transection plane [74]. Otherwise, a more recent randomized trial from the same team was not able to show a real difference between the traditional techniques and the LigaSure vessel sealing system [75]. The instrument is available for both laparotomic and laparoscopic surgery [76]. Furthermore, the use of LigaSure System is not correlated with an increase of the rate of postoperative bile leaks and in some studies bile leakage was nihil [77] and that proves its effectiveness in obliterating also bile vessel. D: after the application the coagulated tissue often sticks to the instrument's jaws causing new bleeding when the device is moved away; BVSD seems to be less effective in presence of cirrhosis for two reasons: first the portal hypertension correlated with cirrhosis causes thinning of the dilated portal vein's walls and makes their obliteration less effective; second cirrhosis makes crushing technique difficult and the hepatic tissue between the blades may disperse the power applied causing vessel to bleed; moreover, it seems to be ineffective in cystopericystectomy [78] (even if some surgeons sustain its effectiveness in this surgery [79]).

2.1.7. Water Jet Scalpel: WJS. The WJS was introduced in 1982 by Papachristou [80]. The device consists of a pressure generating pump and a flexible hose connected to the hand piece. The liquid (saline solution) flows at a steady stream and is projected through the nozzle at the tip of the hand piece. The jet hits the liver at the desired line of transection and washes away the parenchyma, leaving the intrahepatic ducts and vessel undamaged, then the vascular and bile structures can be legated and the transection plane coagulated. The tip is reinforced by a suction tube which removes excess fluid, besides splashing is avoided by covering the area of dissection with a transparent sheet or a Petri dish. Compared to the CUSA, the water jet leaves a smoother cut surface and little hepatic degeneration or necrosis at the borders.

A: WJS can dissect, offering excellent visualization, and is effective also in the cirrhotic liver. In the only available prospective randomized trial of water jet in the literature, in which 31 patients underwent liver resection using water jet and another 30 patients underwent liver resection using CUSA, water jet transection reduced blood loss, blood transfusion, and transection time compared with CUSA [81]. Water jet techniques are quite good for dissecting out major hepatic veins when tumors are in proximity. This allows for delineation of hepatic veins, particularly at the junction with the inferior vena cava, and prevents positive margin.

D: WJS cannot coagulate or realize haemostasis and some studies demonstrate that it cannot achieve a reduction of intraoperative blood loss and operating time if compared with traditional techniques [82, 83]; using this technique is possible in cancerous seeding of the healthy abdominal organs and infection of the operators by hepatic viruses; moreover, in the literature some cases of gas embolism are described using this device [84]. Furthermore, the instrument may be more effective than the CUSA with respect to operating in the presence of cirrhosis. Papachristou and Barters [80] initially reported that the water jet was likely to be ineffective when there is increased fibrotic tissue. Later papers, however, describe successful resections with cirrhosis by using higher jet pressures. Une et al. [81] report that one does not need to use higher water jet pressures to dissect cirrhotic tissue effectively; instead, the same pressures as for normal parenchyma just need to be applied longer. The major concern of surgeons using the water jet is the associated splash. The latter effect is caused by solution bouncing off tissues. Besides, the obvious infectious concerns of the possibility of contaminating operating room personnel, the splash, bring up the notion of the possibility of cancerous seeding. This possibility must be considered in operations for malignancy and one needs to take additional care not to be exposed to the gross tumor during the dissection.

2.1.8. Staplers. Staplers can be used in liver surgery for control of inflow and outflow vessels, or to divide liver parenchyma [85, 86]. The stapler is rarely used as the principal instrument in hepatic resection. The device can add speed to the operation in open or laparoscopic surgery. Its primary use is for achieving control of hepatic vasculature, particularly the hepatic veins. Biliary radicals can be incorporated efficiently into the staple line. Division of the hepatic veins with a stapler as opposed to direct ligation proffers several advantages. First, it eliminates the risk of dissecting the hepatic veins and minimizes the risk of slipped ligature. Furthermore, the stapler simultaneously divides multiple venous branches, especially on the right side, that are too short to allow for a safe, rapid and more traditional ligation.

It is particularly useful in dividing the major trunk of hepatic veins or the middle hepatic vein deep in the transaction. Vascular staplers also can be used to divide the hepatic duct pedicle in the right or left hepatectomy [7]. The procedure starts by dividing the liver capsule by diathermy, the use of a stapler for transection of the liver parenchyma, followed by fracturing the liver tissue with a vascular clamp in a stepwise manner and subsequently divided with an ENDOGia vascular stapler. In a large series of 300 stapler hepatectomies, including 193 major hepatectomies, mortality of 4% and morbidity of 33% were reported which is comparable with conventional liver resection techniques. Vascular control was necessary in only 10% of the series, with an overall median blood loss of 700 mL [87]. Although the technique appears attractive, the financial cost is a serious drawback. One problem associated with the use of a stapler for liver transection is the increased risk of bile leak, since the stapler is not very effective in sealing small bile ducts [88]. Moreover, the surgeon must also be selective in the use of a stapler for the treatment of tumors particularly near the hilum in order to obtain sufficient margin. In case of stapler malfunction, the surgeon should be ready with

a backup technique to achieve vein control in case of a sudden hemorrhage.

2.1.9. Habib's Technique. This technique, invented by Habib in 2002, is also known as bloodless hepatectomy technique [10, 89]. Resection is conducted using cooled tip radiofrequency probe that contains a 3 cm exposed tip to coagulate liver resection margins. Once a 2 cm wide coagulative necrosis zone is created by multiple applications of the probes in adjacent zones and at different depths, the division of the parenchyma with a surgical scalpel is possible. Both the remnant liver and the removed specimen have on the margin of resection a portion of necrotic coagulated liver 1 cm thick.

A: Habib's technique allows hepatic resections with marginal blood loss, without any vessel occlusion technique or intra- or postoperative transfusions. In a preliminary study of 15 cases of mainly segmental or wedge resection reported by Weber et al., the mean blood loss was only 30 ± 10 mL, and no complications such as bile leakage were observed [89]. Another group also reported low blood loss using this technique in liver resection [90]. Haemostasis is obtained only by RF thermal energy: no additional devices like stitches, knots, clips, or fibrin glue are needed [10, 89, 91, 92]; it is effective also in the cirrhotic liver and the 1 cm thick of burned coagulated surface assures margins free from tumour. The technique has the advantage of simplicity compared with the aforementioned transection techniques.

D: Habib's technique cannot be applied near the hilum or the cava vein for fear of damaging this structures and because the blood flow of large vessels subtracts RF energy and involves an incomplete coagulative necrosis [93, 94] (up to now the technique has been experienced only for segmental resection); the 1-cm-thick of burned coagulated layer in the surface involves the loss of part of healthy parenchyma and a higher rate of postoperative abdominal abscesses [92, 95]. Moreover, one potential disadvantage of this technique is the sacrifice of parenchymal tissue in the liver remnant, with a 1 cm wide necrotic tissue at the transection margin, which may be critical in cirrhotic patients who require major liver resection.

2.1.10. Chang's Needle Technique. This technique presented by Chang in 2001 [96] is based on the utilization of a special instrument equipped with an 18 cm straight inner needle with a hook near its top; Chang needle can be applied repeatedly to make overlapping interlocking mattress sutures with N° 1 silks along the inner side of the division line. After this phase, liver parenchyma can be divided directly by scissors, electrocautery or traditional resection methods applying new suture only for tubular structures of significant size.

A: Chang's needle technique can be safely used without vascular occlusion, without any other hemostatic technique thus obtaining a reduction in blood trasfusion rates. This method seems to be capable of reducing both intraoperative blood loss and resection time; besides it is surely cheap and is reported to be simple too [43].

D: it cannot be applied if the lesion is too close to inferior cava vein [97].

2.1.11. Gyrus PlasmaKinetic Pulsed Bipolar Coagulation Device. Gyrus (Gyrus Medical Inc., Maple Groves, MN, USA) is a bipolar cautery device which seals the hepatic parenchyma using a combination of pressure and energy that results in the fusion of collagen and elastin in the walls of the hepatic vasculature and bile ducts [98]. The device can reliably seal vessels up to 7 mm in diameter minimizing the amount of blood loss during the transection of the liver. Thermal spread and sticking to tissues is reduced by a cooling period after each pulse as the impedance of the coagulated tissue increased. This instrument has been widely used in previous gynaecological procedures and its use in liver surgery is relatively new. It could be used in a similar manner to the clamp-crush technique to transect hepatic parenchyma. After incising the hepatic capsule with Bovie, the instrument is inserted into the liver in an open manner and bipolar energy is applied as the forceps are slowly closed over the parenchyma. In a recent series, median blood loss rate is compared favourably with those in several large series using the traditional clamp-crush technique [99]. Moreover, blood loss and transfusion rates were comparable with those cited in recent report of alternative parenchymal transaction, as showed by results of Tan et al. [100]. In this study, Gyrus is compared favourably with Harmonic scalpel in terms of bile leakage and the author underlined the concorrential cost of the device. Moreover, it seems to be useful even in case of cirrhotic patients. Corvera et al. [98] have also reported the use of the Gyrus device in cirrhotic livers comparing it to the clamp and crush technique. They evaluated five patients in each group showing similar results between the two groups in terms of operating time, blood loss, and major postoperative complications.

2.1.12. Haemostasis Techniques. Coagulation of vessels over 1 mm of diameter can be achieved by positioning clips or sutures before division, or using devices like LigaSure, TMFB, or HS for their target vessels or staplers for the largest veins. Clips and sutures are used especially during transaction through traditional techniques.

During and after liver's transaction, haemostasis of the vascular structures under 1 mm of diameter is another important concern of the surgeon: firstly because the continuous bleeding from the little vessels in the parenchyma represents a considerable part of intraoperative blood loss, and secondly because it makes hard for the surgeon to visualize the surgical field. The stop of tearing small vessels that causes oozing from the cut surface can be achieved with normal monopolar or bipolar electrocoagulator, better if equipped with saline irrigation that makes them less traumatic and avoids formation of sticky coagulum. An alternative is represented by employment of Argon Beam Coagulator or TMFB that probably is the best device for stopping tearing of small vessels on the cut surface of the liver.

After the resection, another two precautions can be taken: application of mattress sutures for providing a mechanical compression of the bare surface and application of biological glue for realizing complete haemostasis through a chemical/biological action.

2.1.13. Choice of Surgical Strategy. The choice of surgical strategy is based on the preoperative evaluation and on the now indispensable intraoperative ultrasonography (IOUS); in fact several studies have demonstrated that the IOUS is capable of changing surgical strategy in over 40% of cases finding new lesions or diagnosing as inoperable lesions those which were thought as operable at the previous evaluation [101–104]. The kind of surgical strategy chosen for the intervention on the base of the effects strongly influences the operative outcome and the amount of operative blood loss. The most considerable aspect is the amplitude of the resection: a large resection like a right hemihepatectomy (or another typical resection) involves a higher bleeding and a risk of complications. From this point of view, the choice of segmental or wedge limited resections, when they are possible in respect of radical oncology standards, has to be considered as the best option [105, 106]. Usual surgical margins for removal of liver tumours are 1 cm of healthy parenchyma surrounding the lesion. Kokudo et al. in 2002 demonstrated that for colorectal metastases the surgical margin can be, in particular situations, lowered to 2 mm with increase of the pathology recurrence rate from O% for 5 mm margin to 6% for 2 mm margin [107].

This finding, combined with a contrast-enhanced IOUS during the resection, could be a rationale incentive for practising limited resections [108–110], and the possibility of an accurate investigation of the remnant liver through the IOUS.

2.1.14. Drug Administration for Reducing Intraoperative Blood Loss. Liver resection may cause a variable degree of hyperfibrinolytic states; this phenomenon occurs in the days immediately after hepatectomy and is more pronounced in patients with a diseased liver or in patients who have undergone to a wider hepatectomy extent [111–116]. So some authors propose the utilization of drugs with antifibrinolytic effect like Aprotinin that is reported to be capable of reducing intraoperative blood loss (especially during liver resection time) and transfusions [117–119]. Other authors propose utilization of the cheaper Tranexamic acid reporting similar results [120]. Although a theoretical risk of thromboembolic complications is present, no adverse drug effects like deep venous thrombosis, pulmonary embolism, or other circulatory disturbances were detected in both these studies.

3. Comparison of Different Liver Transection Techniques

The choice of transection techniques is currently a matter of preference for surgeons, as there are few data from prospective randomized trials that compared different techniques. It has been shown in small prospective randomized trials that clamp crushing or water jet may be preferable to CUSA in terms of quality of transection or speed of transaction [1, 121]. However, the results of these trials remain to be validated by larger-scale trials. CUSA dissection is still a widely used technique worldwide. Recently, a randomized trial compared four methods of liver transection, namely, clamp crushing, CUSA, Hydrojet, and dissecting sealer, with 25 patients in each group [122]. In that study, clamp crushing was associated with the fastest transection speed, lowest blood loss, and lowest blood transfusion requirement. Furthermore, clamp crushing was the most cost-effective technique. However, in that study, clamp crushing was performed with the Pringle maneuvre, whereas the other techniques were performed without the Pringle maneuvre. This might have resulted in bias in favor of clamp crushing. Another recent comparative study between clamp crushing technique (CRUSH), ultrasonic dissection (CUSA), or bipolar device (LigaSure) failed to show any difference between the three techniques in terms of intraoperative blood loss, blood transfusion, postoperative complications, and mortality [73]. Further prospective randomized studies are needed to determine which transection technique is the best. Moreover, a recent review of the Cochrane conclude that clamp-crush technique is advocated as the method of choice in liver parenchymal transection because it avoids special equipment, whereas the newer methods do not seem to offer any benefit in decreasing the morbidity or transfusion requirement. Otherwise in the comparison of different techniques, apart from the efficacy in transaction with low blood loss, the relative speed of transection and the potential complications are other parameters to be considered [121]. Furthermore, the use of special instruments for transection is costly, especially when two instruments are used in combination for transection and hemostasis. It is difficult to compare the relative cost of different transection instruments because some are reusable whereas others are designed for single use, and the cost of the same instrument varies substantially in different countries. Nonetheless, the cost of these various techniques should play a part in the surgeon's decision as to whether to use them or not.

3.1. The Role of the Anaesthetist. Patients who are subjected to liver surgery are usually pre- and intra-operationally treated with infusion of liquids, plasma expanders, and blood products: normally hepatic resections are in fact conduced in condition of euvolaemia or hypervolaemia to protect patients from the risk of consistent haemorrhage and haemodynamic's instability.

Despite this idea, several studies have demonstrated that a condition of low central venous pressure (LCVP) can reduce bleeding, recourse to vessel occlusion techniques, and transfusions during resection [111–113]. It has been scientifically demonstrated that intraoperative blood loss is correlated with inferior retrohepatic vena cava pressure [114].

Mendelez obtained very low blood loss results in major hepatic resections and managed to keep the CVP under

5 mmHg: this is possible with abstention from practising any infusion but intraoperative liquid infusion at the low speed of 75 mL/h and without any drug administration but employing hypotensive effects of normal anaesthetics (like Isoflurane, Morphine and Fentanyl). It is obvious that LCVP technique needs a strict monitoring of several parameters: in particular, systolic arterial pressure has constantly to be kept over 90 mmHg and diuresis over 25 mL/h. After the specimen is removed and after the realization of complete haemostasis starts, the infusion of liquids, and, if necessary, of plasma expanders and blood products until euvolaemia is obtained and haemoglobin value is over 8–10 g/dL [115].

LCVP has to be abandoned in case of uncontrollable haemorrhage (over 25% of total blood volume) or application of total vascular exclusion technique. Mendelez using LCVP reports a 0,4% rate of gas embolism [116]. This illustrates the importance of collaboration between surgeons and anaesthetists for a successful hepatectomy.

4. Conclusions

Improvement in the techniques of liver transection is one of the most important factors for improved safety of hepatectomy in recent years. The use of intraoperative ultrasound aids delineation of the proper transection plane and allows to transect tumor close to main vessels without bleeding. Clamp-crushing and ultrasonic dissection are currently the two most popular techniques of liver transection. The role of new instruments such as ultrasonic shear and RFA devices in liver transection remains unclear, with few data available in the literature.

The role of vascular exclusion including Pringle's maneuvre seems to be decreasing with improved transection technique. However, it remains a useful technique in reducing bleeding from inflow vessels, especially for surgeons with less experience in liver resection, and recent results show safety of this technique even for prolonged total time of ischemia. Maintenance of low central venous pressure remains an important adjunctive measure to reduce blood loss in liver transection.

As clear data for comparison of various liver transection techniques are lacking, currently the choice of technique is often based on the individual surgeon's preference. However, certain general recommendations can be made based on existing data and the author's experience. Clamp-crushing is a low-cost technique but it requires substantial experience to be used effectively for liver transection, especially in the cirrhotic liver. CUSA can be used in both cirrhotic and noncirrhotic liver, is associated with low blood loss, and has a well-established safety record, with low risk of bile leak. It is particularly useful in major hepatic resections when dissection of the major branches of the hepatic veins is required, or in cases where the tumor is in close proximity to a major hepatic vein, as it allows clear dissection of the hepatic vein from the tumor. The main disadvantage of the CUSA technique is slow transection.

Newer instruments such as the Harmonic scalpel, LigaSure, and TissueLink Dissector enhance the capability of hemostasis and allow faster transection. However, they lack the preciseness of CUSA in dissection of major hepatic veins, and HS more than others may be associated with increased risk of bile leak. Moreover, they are particularly useful in laparoscopic liver resection. They can also be used in combination with CUSA for sealing of vessels, but this increases the cost substantially. RFA-assisted transection is probably the most speedy liver transaction technique. However, the risk of thermal injury to major bile duct is a serious concern and its use is probably restricted to minor resection. Gyrus and Aquamantys are relatively new instruments and the literature does not allow to draw any conclusion about their efficacy and safety.

The experience of the surgeon in practising hepatic surgery, whatever is the method to perform it, is still a factor of primary importance. In spite of that, the advent of new diagnostic instruments, new devices for resection and coagulation, a better knowledge of the liver's anatomy and pathology, and a closer collaboration with the anaesthetist make the hepatic surgery a kind of surgery more defined and rational. From this point of view, new studies based on the use of different surgical strategies, association of different devices, and employment of different diagnostic and anaesthetic techniques are desirable.

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Review Article

Contemporary Strategies in the Management of Hepatocellular Carcinoma

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Liver transplantation is the treatment of choice for selected patients with hepatocellular carcinoma (HCC) on a background of chronic liver disease. Liver resection or locoregional ablative therapies may be indicated for patients with preserved synthetic function without significant portal hypertension. Milan criteria were introduced to select suitable patients for liver transplant with low risk of tumor recurrence and 5-year survival in excess of 70%. Currently the incidence of HCC is climbing rapidly and in a current climate of organ shortage has led to the re-evaluation of locoregional therapies and resectional surgery to manage the case load. The introduction of biological therapies has had a new dimension to care, adding to the complexities of multidisciplinary team working in the management of HCC. The aim of this paper is to give a brief overview of present day management strategies and decision making.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. Ninety percent of primary liver cancers are HCC, the majority of which develop on the background of cirrhosis. Over the past decade, medical management of the patient with chronic liver disease has improved. In parallel, the prevalence of hepatitis B (HBV), hepatitis C virus (HCV), alcohol related liver disease, and NASH has increased and combined with an ageing population has led to a surge in the number of cases worldwide [1–3]. As a consequence, HCC is an important complication of cirrhosis and a leading indication for liver transplantation (LT), accounting for approximately a third of patients on transplant waiting lists [4]. The introduction of surveillance using alphafetoprotein and ultrasound has led to the earlier recognition of HCC and increases the therapeutic options available [5]. In the absence of treatment the overall 5-year survival is <10% [6]. These include LT, resection, locoregional, and systemic therapies. For a solitary HCC with preserved liver function and low hepatic vein pressure gradient, liver resection still remains the first choice.

Historically, survival rates were 35–62% at 3 years and 17–50% at 5 years for patients with cirrhosis undergoing resection for HCC [6, 7]. However, tumor recurrence rates were high, up to 70%, and progression to liver failure was common [6, 8–10]. LT is an attractive treatment option as it treats both the cancer and underlying liver disease. In the 1980s, patients presenting with large HCC were considered good candidates for LT as they were in better condition than patients with chronic liver disease and were more likely to survive the perioperative period but they had large or multifocal tumors. This resulted in a high recurrence rate of up to 65%, a 5 year survival of 10–35%, and a median survival of those with recurrence of 6 months, coupled with increasing demand for donor livers led to a more restrictive selection process [11–13]. Recognition that small tumors appeared to fare better after LT led Mazzaferro to introduce the Milan criteria to select patients leading to improved survival with low rates of tumor recurrence [14]. By adhering to the Milan criteria of undertaking LT for HCC with a solitary tumor $\leq$ 5 cm or 3 tumors $\leq$ 3 cm each, a 5 year survival greater than 70% and recurrence rates of <10% were produced.

2. Staging

A staging system for HCC poses problems because the presence of liver disease and tumor varies due to the different epidemiological backgrounds and risk factors. The ideal staging system needs to include prognostic information regarding both the cancer and liver functional status and take account of clinical factors that influence response to treatment. The TNM classification is an oncology standard useful in conjunction with the presence of microvascular invasion of examined resection or explanted tumors/liver and provides information regarding the risk of tumor recurrence but does not take account of the liver functional status. As TNM requires pathological data (microvascular invasion) and only 20% HCC are resected for which it is good at discriminating stages for, its usability is limited. The Okuda staging system has been widely used since 1985. It uses four criteria of ascites, albumin, bilirubin, and tumor size to assess liver functional status and tumor stage. It is a good system for stratifying advanced/symptomatic disease but less useful in early stage to guide treatment choices. Other available systems are the French classification, the Cancer of the Liver Italian Program (CLIP) classification, and the Barcelona-Clínic Liver Cancer (BCLC) staging system; the Chinese University Prognostic Index (CUPI score) and the Japan Integrated Staging (JIS) or bm-JIS if biomarkers are included [15]. The CUPI and CLIP scores mainly stratify patients at advanced stages; only two include prognostic variables (BCLC, CUPI) and only one allocates treatment according to specific prognostic subclasses (BCLC). The BCLC is emerging as the standard staging system for HCC in the West and has been externally validated and incorporates prognostic variables related to tumor (size, number, vascular invasion, N1, M1), liver function (Child-Pugh), and health status (ECOG-Eastern Cooperative Oncology Group Performance Status). As well as incorporating variables that influence therapy such as bilirubin, portal hypertension, and presence of symptoms to assist in treatment decision making (see Figure 1).

3. Liver Transplant

LT is the treatment of choice for small multifocal HCC ≤ 3 tumors and ≤ 3 cm or a single tumor ≤ 5 cm with significant liver functional impairment. Better selection of patients has improved 5 year survival to >70% and recurrence <10%. The major limitation to LT as treatment for HCC is the scarcity of cadaveric donors and the associated waiting time that results in a 20% drop-out rate and potentially increases the risk of recurrence from extension of vascular invasion. The use of tumor size and number to try to reflect tumor biology has been successful. However, it is clear that some patients with favourable "biology" are excluded. A number of groups have tried to expand indications beyond the Milan criteria and claim to achieve similar survival rates [16, 17]. The University of California San Francisco (UCSF) criteria are probably the best known and include one tumor ≤ 6.5 cm or multiple tumors of which the largest is 4.5 cm and the sum of all diameters is ≤ 8 cm [16]. More recently the up-to-7 criteria, where the HCC scores 7 based on the sum of the largest tumor (diameter cm) and the total number of tumors, have been introduced [17]. The majority of the studies supporting extension of the Milan Criteria are based on retrospective histological analysis of the tumor burden in the explant liver and have not been validated prospectively [16–19].

Another area where the principles of the Milan Criteria have been challenged is in salvage LT. Salvage LT has been advocated by some to manage HCC within Milan Criteria after resection [20]. In selected cases, similar overall 5 year survival for salvage LT as primary LT for HCC has been achieved (provided the comparison is from time listed for LT rather than date of LT, that is, intention to treat bias). There is continuing debate regarding whether previous resection compromises the subsequent LT [21]. Other groups have found salvage LT to have a high operative mortality, 23.5% versus 2.1% for primary LT, higher recurrence rates, and poorer overall 5 year survival of 41% [22]. Salvage LT remains controversial at a time of a limited resource with tumor characteristics, background liver (cirrhotic or noncirrhotic), and centre experience appearing to be the main determinants of recurrence and survival.

An alternative strategy to expanding the criteria for LT is to downstage to within Milan Criteria aiming to achieve patient survival and recurrence free survival rates similar to those treated at an earlier stage. This is distinct from bridging therapy. Bridging therapy is utilised to maintain the tumor within listing criteria while a suitable graft is awaited for on the waiting list. Bridging therapy is a widely accepted practice whereas downstaging for LT is not [23, 24]. To be eligible for downstaging locoregional therapy, there should be no radiological evidence of vascular invasion. There is no consensus limit to tumor number or size [25]. Predictors of downstaging failure are tumors with an infiltrative pattern [26] and an AFP $>$ 1000 ng/mL [27]. There is evidence to suggest that downstaging of HCC to within Milan Criteria can produce reasonable results [25, 27]. But the data is difficult to interpret as the studies utilise different inclusion criteria (tumor size and number), locoregional therapies either individually or in combination, and endpoints. Current published data reveal that after downstaging, surgical resection rates vary widely between 7% and 18% producing 5 year survival rates of between 25% and 57% [28] and LT rates range between 24% and 90%, with an intention to treat post HCC treatment survival of between 60% and 70% at 3 years [27, 29, 30].

Living donor LT (LDLT) is a good graft option for HCC as it allows neoadjuvant treatment to be organized around a LT. It provides a high-quality graft and removes a competing HCC recipient from the waiting list. But higher recurrence rates and reduced survival have been reported when compared to cadaveric LT [31–33]. Explanations for this observation include growth factors released from the regenerating liver may stimulate cancer cell growth. The shorter waiting time for LDLT may remove the observation period that occurs on the waiting list to assess tumor biology and a 3 month cooling off period has been advocated before undertaking LDLT. Surgical oncological clearance may also be compromised as the IVC has to be preserved for LDLT

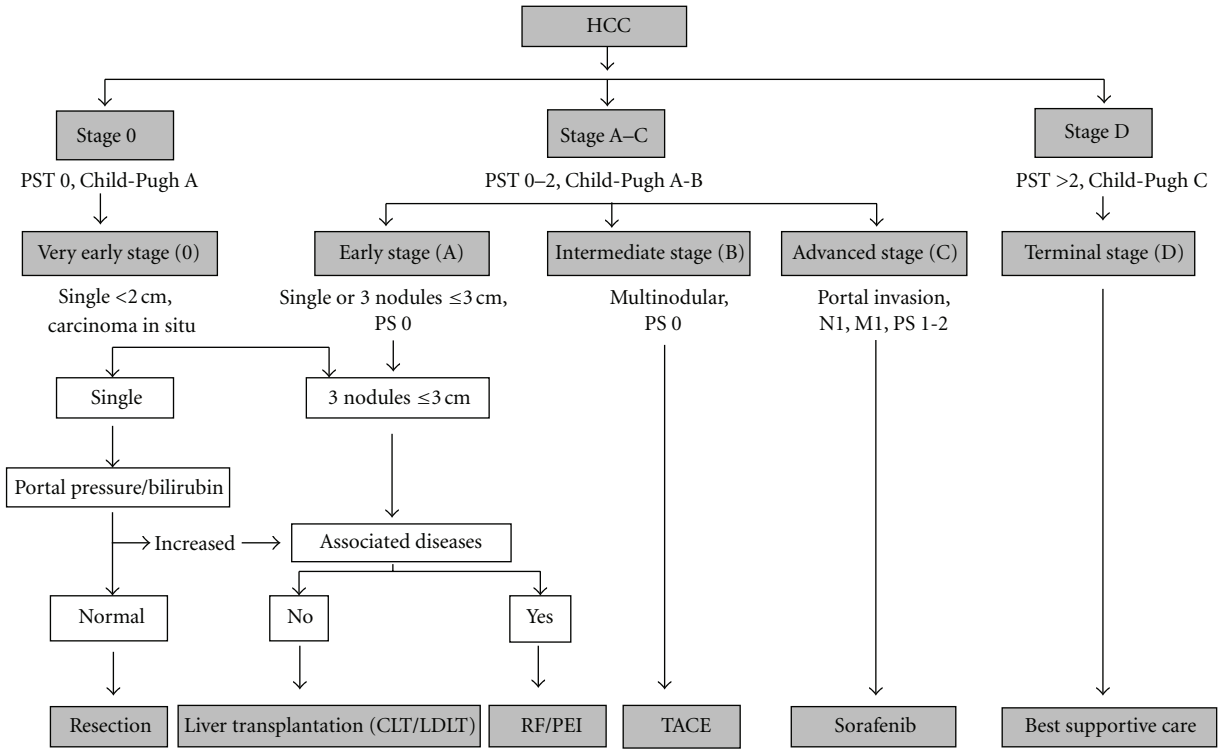

Figure 1: The Barcelona-Clínic Liver Cancer (BCLC) staging system for HCC. M: metastasis classification; N: node classification; PST: performance status; RFA: radiofrequency ablation; TACE: transarterial chemoembolization.

[34]. In addition, an element of institutional bias may lead to LDLT in HCC with a higher risk of recurrence. On multivariate analysis of published studies on LDLT versus cadaveric LT, graft type, and waiting time have not been found to be significant risk factors for recurrence post LT. If LDLT is undertaken for HCC outside regional criteria and the graft fails retransplantation with cadaveric LT is ethically contentious [35]. The donor risk and the degree of benefit to the recipient needed to justify LDLT for advanced HCC are still undetermined and for now many centres have adopted the same criteria/therapeutic goals for LDLT as cadaveric LT [36].

4. Liver Resection

Resection is the treatment of choice in noncirrhotics. Noncirrhotic HCC accounts for 5% of cases in the West and 40% of cases in Asia. Patients with cirrhosis suitable for resection need preserved liver function and a hepatic venous pressure gradient ≤10 mmHg. Anatomic resection is advocated by some as being more preferable to nonanatomic, as it is thought to produce better outcome by eliminating intrahepatic metastases in the related portal vein tributary [37]. In patients with cirrhosis selected on liver functional status, the main predictors for survival are tumor size, multiplicity, and vascular invasion. Five-year survival for tumors ≤2 cm, 2–5 cm, and >5 cm are 66%, 52%, and 37%, respectively. For single tumors the 5 year survival is 57% and for multiple 26% but some centres are achieving >50% in multiple HCC within the Milan Criteria but otherwise are not suitable for LT [38]. Recurrence remains problematic occurring in 70% at 5 years; true recurrence/intrahepatic metastases generally occur within 2 years of resection; if greater than 2 years it is generally regarded as a de novo tumor or late recurrence [39]. At present there is no evidence that neoadjuvant/adjuvant therapy has any efficacy in reducing recurrence after resection [40]. Downstaging locoregional therapy can be employed to facilitate resection in disease which is initially regarded as unresectable and can achieve reasonable outcome, with 5 year survivals of 25–67%, with the possibility of cure [28]. Preoperative portal vein embolisation can be employed to increase future remnant liver volume to allow more extensive resections to be undertaken but the complication rate in cirrhotics is 10–20% and its effectiveness in this patient group is not fully established [41]. A laparoscopic approach to resection in cirrhotics has been proposed by some to reduce the operative insult and the risk of decompensation [42].

5. Locoregional Therapy: Ablation, TACE, and Radiation

There are a number of different locoregional strategies available or being developed but the largest experience is with transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). Percutaneous ethanol injection (PEI) was the first chemical ablative technique utilised. When applied to small tumors <2 cm PEI produces 90% necroses and a 5-year survival of 47–53% but is limited by high

recurrence rates of approximately 40%. Chemical ablation has now been superseded by thermal techniques such as radiofrequency ablation (RFA). RFA is the most well-studied alternative to PEI producing better local tumor control with a 2 year recurrence of 2–18% and a 5 year survival of 40–70% or better when the treatment groups have been selected [43]. Meta-analyses of randomised control trials have confirmed that RFA is a more effective way to obtain local tumor control and survival benefit compared to PEI, establishing it as a standard locoregional treatment [44, 45].

RFA can be performed percutaneously, laparoscopically, or at open surgery depending on tumor location [46, 47]. RFA is effective for early small HCC <3 cm when resection or LT are not feasible [48–51], whereas larger tumors may be inadequately treated. Overall 10–25% of tumors will not be suitable for RFA because of location such as subcapsular, adjacent to the gall bladder or major vessels which increases the risk of complication and inadequate ablation because of heat sink. The recurrence rate after RFA for selected early small HCC can be comparable to that of surgery [50, 51]. In highly selected HCC < 2 cm RFA has the potential to be curative with a rate of complete response approaching 97% and a 5 year survival of 68%. However, randomised control trials of RFA against resection for small HCC < 3 cm have failed to show that RFA is as effective as resection but the majority of studies were underpowered or had incomplete follow up [49, 52]. Increasingly, RFA is being considered as an alternative initial "curative" treatment option for small centrally placed HCC as it offers the advantages of preserving parenchyma, potentially removes competition from the transplant waiting list and based on location, effective tumor necrosis can be obtained [43, 48].

Solitary HCC > 3 cm but <5 cm RFA becomes less effective. But when TACE followed by RFA for this size tumor is applied, the therapeutic effect of RFA is significantly increased and reduces tumor progression rate to 6% compared to 39% for RFA alone [53]. In larger HCC > 5 cm outside LT criteria or not suitable for resection, ablative strategies may not work in a predictable manner. TACE also has inconsistent results and no advantage has been demonstrated by combining therapies [54]. When RFA is not suitable either because of tumor location or size, novel thermal or nonthermal ablative techniques may overcome the limits of RFA. Promising thermal ablative strategies include microwave producing large areas of ablation with less heat sink and high intensity focused US (HIFU) that can be used in patients with ascites. Alternative non thermal ablative techniques of interest include irreversible electroporation (IE). Ablative technology is improving and further experience will determine its applicability. In assessing the effectiveness of ablation radiologically, the widely used RECIST (the response evaluation criteria in solid tumours) has limitations as it includes both necrotic and viable tumor areas [55] and the modified RECIST that includes the assessment of viable tumor showing uptake in the arterial phase is more reliable.

Based on a meta-analysis TACE is emerging as the standard of care for asymptomatic HCC outside Milan criteria [56], demonstrating improved survival compared to best supportive care. A partial response of 15–55% can be observed producing a survival benefit, increasing median survival time from 16 months to 20 months with 49% survival at 2 years [56]. But individually the studies did not clearly demonstrate a benefit, mainly because of heterogenous patient study groups and varying TACE techniques. This implies that good results with TACE are achieved when it is used on a selective basis. Generally TACE is not suitable in decompensated liver disease where there is ascites or jaundice to the avoid major complications and minimize treatment related deaths to less than 2% [57]. For optimal results TACE needs to be as selective as possible, producing sustained and high localised concentrations within the tumor minimizing systemic exposure. Alternative ways to be delivering chemotherapy instead of the standard ethiodized oil (lipiodol) suspensions are drug-eluting beads [58]. In the PRECISION V trial [59], a randomized control trial, comparing drug-eluting beads with doxorubicin to conventional TACE with doxorubicin found it was better tolerated, with reduced liver toxicity and improved treatment response. Owing to the improved safety and tolerance drug-eluting beads could be applicable in higher risk patient groups. Further ways of optimising the therapeutic benefit of TACE is by combining with systemic drugs. Using agents that target the angiogenic pathways that are switched on by the local hypoxia produced by TACE is being evaluated [45]. Generally, if there is no response after two TACE sessions, alternative treatment strategies should be considered, which in the majority will be systemic therapy. In highly selected patients consideration should be given to combination of treatments such as ablation/radioembolization.

Advanced HCC that is symptomatic, exhibiting vascular invasion and/or has extrahepatic disease have a short median survival of 6 months with 25% surviving a year [60]. Systemics are often the only treatment option for palliation but there is a subset that benefit from locoregional therapy such as where vascular invasion is limited to a venous branch receiving intra-arterial therapies such as TACE [61] or radioembolization [62]. Radioembolization using yttrium-90 (90Y) labelled microspheres a beta emitter, appears promising, and may also be effective as a precursor to radical therapy with outcomes similar to TACE [30, 63] and Sorafenib [64]. There is a need to be aware of intestinal and lung shunting which may provoke serious complications. There is a minimal embolic effect so when there is main portal vein involvement and TACE is contraindicated radioembolization with yttrium may be a good option. In the absence of portal vein involvement radioembolization in Child A survival is 15.5 months, Child B is 13 months, with a portal vein involvement survival of both Child A + B being 5.6 months [65] with 25–50% response rates [64].

Cyberknife is a new stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) in combination with a robotic system that tracks the tumor during respiration and is able to deliver high dose radiation accurately sparing adjacent normal tissue in a small number of fractions. A number of studies in HCC not suitable for standard locoregional treatment or resection have reported promising results. In HCC < 100 ml progression free survival

rates at 6 months, 1 year, and 3 years of 83%, 72%, and 68% respectively, with overall survival at 1 year, and 3 years of 92.9% and 58.6% have been reported. It also has utility as local salvage treatment after TACE achieving local control in 95% [66]. To this date no serious SBRT related toxicities being reported [67–69] but it is not clear whether it can be applied to patients with more severe liver diseases as its threshold for tolerance is not defined.

6. Systemic Therapies: Antiviral Therapy, Immunosuppression, Biologicals, and Chemotherapy

Worldwide 78% of HCC are viral related with 53% attributed to HBV and 25% to HCV [70]. Risk of HCC recurrence after treatment is increased with progression of active hepatitis and fibrosis. Antiviral therapy is used as an adjuvant treatment with the aim to reduce viral load and fibrosis with the aim of halting progression of viral induced liver disease and reducing the risk of further HCC developing. Hepatitis B (HBV) infection increases the risk of HCC recurrence particularly for the patient who is HBeAg + and/or has a high serum HBV DNA level [71, 72]. Treatment with nucleoside analogues entecavir or tenofovir suppresses HBV DNA levels improving liver function in decompensated liver disease and may reduce the risk of HCC development over time [73]. HBV antiviral therapy reduces risk of recurrence by 41% and overall mortality by 73%, mainly because death from liver failure is reduced by 77% [74]. Use of longterm lamivudine treatment resistance can occur in 70% over 5 years has given way to alternative nucleoside analogues such as entecavir, telbivudine, and nucleotide analogues such as tenofovir but longterm data is lacking for their effect on reducing HCC recurrence.

Chronic infection with HCV appears to increase the rate of HCC development in a similar way to HBV. The risk does not change with genotype (G) but a recent meta-analysis suggests that HCV G1b maybe more at risk of HCC transformation [75]. Meta-analysis of adjuvant alpha IFN shows reduction in HCC recurrence and mortality in curatively ablated viral hepatitis related HCC. Individually these studies report no effect. Antiviral potency and the ability to produce a sustained viral response (SVR) in HCV appear to be associated with reducing the risk of HCC recurrence [76]. More longterm data is needed from the newer protease inhibitors (boceprevir, telaprevir) to determine whether the higher SVR they are able to produce translates into lower risk of HCC longterm.

Immunosuppressive agents compound malignant behaviour as immune surveillance for cancer cells is impaired. Mammalian target of rapamycin (mTOR) inhibitors, for example, Sirolimus is an exception to this rule. mTOR is overexpressed in approximately 2/3 of HCC making it an attractive therapeutic target [77]. To establish whether the immunosuppressive regime affects recurrence rates, data from the SiLVER Study is awaited. The SiLVER Study is a randomised multicenter clinical trial comparing Sirolimus containing to a mTOR inhibitor free immunosuppressive regimes. The study consists of a 3-year enrolment period and a 5-year followup. At present, there is little evidence on whether the immunosuppression regime should be completely changed to a mTOR inhibitor or whether these agents should be added to the preexisting immunosuppressive regime when recurrent HCC presents post LT [35, 78, 79]. CNI exposure should be minimised as there is evidence that this reduces the risk of tumor recurrence long term [80].

HCC is an unique chemoresistant tumor and until 2007 no systemic drug was recommended for its management. In the early 1990s, a number of randomised controlled studies assessed the role of adjuvant chemotherapy but no benefit or efficacy was demonstrated. Multiple agents have been assessed but doxorubicin, an anthracycline, has been most rigorously studied [81, 82]. The main patient groups that should be considered for adjuvant chemotherapy are those being transplanted for extended criteria or have a high risk of recurrence based on the explant pathology. As patients selected for LT should be at low risk of recurrence the majority will not gain any benefit from routine adjuvant chemotherapy.

Since 2007 Sorafenib, an oral tyrosine kinase inhibitor, has become the standard of care. Based upon the SHARP study that demonstrated Sorafenib improved median survival from 7.9 months to 10.7 months and slowed time to progression from 2.8 to 5.5 months [83]. It is well tolerated with diarrhoea in 8-9% and hand-foot skin reaction in 8–16%, with side effects leading to its discontinuation in 15%. Sorafenib is regarded as the standard therapy for metastatic disease and for HCC progressing despite optimal locoregional therapy [84]. A number of ongoing studies are establishing Sorafenib's adjuvant role in resection, local ablation (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM)), and TACE. Additionally, a phase 1 study is being undertaken in high-risk patients post-LT that on explant are outside Milan criteria with microvascular or macrovascular invasion or histologically poorly differentiated HCC. At present there is no evidence of increased toxicity in LT recipients and Sorafenib can produce a response based on published case reports [85, 86]. Other biological agents entering phase 2 or 3 trials for HCC include EGFR (erlotinib) and VEGFR/FGFR (brivanib) tyrosine kinase inhibitors [87].

7. Conclusions

Management of HCC continues to evolve and interventional radiology in the form of TACE ± RFA increasingly dominates management either as a bridge to LT or to downstage facilitating LT or resection. As locoregional therapy technology advances patients that can be considered either for palliation or potential cure will increase. Criteria for LT listing need to become more sophisticated by incorporating tumor biology in decision making, presently inferred from clinical behaviour but in the future by the use of molecular markers. This will facilitate stratification and individualization of HCC treatment. Ultimately, the aim of LT, irrespective of

disease etiology is to give the maximum benefit from a limited organ pool.

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Review Article

Surgical Options for Initially Unresectable Colorectal Liver Metastases

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Although the frontiers of liver resection for colorectal liver metastases have broadened in recent decades, approximately 75% of these patients present with unresectable metastases at the time of their diagnosis. In the past, these patients underwent only palliative treatment, without the chance of a cure. In the previous two decades, several therapeutic strategies have been developed that render resectable those metastases that were initially unresectable, thus offering the chance of long-term survival and even a cure to these patients. The oncosurgical modalities that are available include liver resection following portal vein ligation/embolization, "two-stage" liver resection, one-stage ultrasonically guided liver resection, hepatectomy following conversion chemotherapy, and liver resection combined with thermal ablation. Moreover, in recent years, certain authors have recommended the revisiting of the concept of liver transplantation in highly selected patients with unresectable colorectal liver metastases and favorable prognostic factors. By employing such therapies, the number of patients with colorectal liver metastases who undergo a potentially curative treatment could increase to 40%. The safety profile of these approaches is acceptable (morbidity rates as high as 45%, mortality rates of less than 5%). Furthermore, the 5-year survival rates (approximately 30%) are significantly increased over those that were achieved with palliative treatment.

1. Introduction

The current treatment for patients with liver metastases from colorectal cancer is multimodal, including liver resection, chemotherapy, targeted therapies (monoclonal antibodies), interventional radiology, and radiotherapy. The complete resection of liver metastases results in 5-year overall survival rates that range from 21% to 58% [1–3], which are significantly higher than those rates that are achieved by nonsurgical therapies (5-year survival rates less than 5%) [4]. Thus, the only potentially curative therapy in patients with colorectal liver metastases (CRLM) includes complete resection of the liver metastases.

At present, CRLMs are considered resectable when the following criteria are met [5, 6]:

(a) the complete resection of all known disease can be achieved,

(b) at least two contiguous liver segments can be preserved, with adequate vascular inflow and outflow, with biliary drainage,

(c) the remnant liver volume is adequate to avoid postoperative liver failure.

In patients with a healthy liver, the volume of the future liver remnant (FLR) should represent more than 25% of the total liver volume (TLV) to avoid postoperative liver failure [7–9]. However, in patients with chronic liver disease or chemotherapy-induced liver injury, a minimum of 40% of the TLV should be preserved [9–12].

Therefore, although the frontiers of liver resection have broadened over the previous two decades [13], approximately three quarters of patients with CRLM are not eligible for an initially curative liver resection (R0) after a preoperative evaluation [14].

The most common causes of the initial unresectability are the following.

(1) A single, very large liver metastasis, the resection of which would not spare a sufficient volume of liver parenchyma to avoid postoperative liver failure.

(2) Multiple bilobar liver metastases, the complete resection of which would not preserve a sufficient volume of functional liver parenchyma.

(3) CRLM involving or located in close proximity to either the bifurcation of the portal vein or the confluence of the three hepatic veins with the inferior vena cava (IVC). In this case, the resection of the liver metastasis would not allow for the preservation of a minimum of two adjacent liver segments with adequate vascular inflow and outflow.

Until 20 years ago, the only available treatment for these patients was palliative chemotherapy, the goals of which were to increase progression-free and overall survival; however, there was no prospect of a cure. Although survival rates increased with the advent of new chemotherapeutics (such as Oxaliplatin and Irinotecan) and targeted therapies (e.g., Bevacizumab, Cetuximab, and Panitumumab), the current survival rates for these cases are still modest compared to those that can be achieved by liver resection. Therefore, several therapeutic strategies were introduced to achieve a complete resection in these patients [15].

2. Therapeutic Options

In Figure 1, we schematically present those situations in which metastases are considered unresectable and the therapeutic options that are available for conversion to resectability.

2.1. Liver Resection Following Portal Vein Embolization/Ligation. In certain instances, although a minimum of two adjacent segments with appropriate vascular inflow and outflow, and biliary drainage can be preserved following the complete resection of CRLM, the volume of the remaining liver parenchyma may be insufficient to avoid postoperative liver failure. Such situations are generally encountered in patients who (1) require a right trisectionectomy, or (2) when a right hemihepatectomy must be performed, but the volume of the left hemiliver is prohibitively small (Figures 1(a) and 1(b)). To avoid postoperative liver failure in these patients, it is advisable to attempt to increase the volume of the FLR prior to the liver resection.

This goal may be achieved by initially performing portal vein embolization (PVE) or ligation (PVL). If the volume of the FLR following a PVE/PVL increases sufficiently to prevent the risk of postoperative liver failure, liver resection should be performed 4–8 weeks later.

This therapeutic strategy is based on the observation that increasing the volume of the FLR improves the function of the residual liver parenchyma following the hepatectomy [16, 17].

The reports of Kinoshita and Makuuchi revealed that the ligation or embolization of the right portal vein induces a process of atrophy-hypertrophy of the liver (increasing the safety of liver resection) in patients with hepatocellular carcinoma or hilar cholangiocarcinoma [18, 19]. Therefore, other authors applied the same procedure in patients with CRLM whose FLR was insufficient to avoid postoperative liver failure [10, 20–22]. The rationale for such an approach is that the embolization or ligation of the right portal branch abolishes the portal inflow into the right hemiliver, leading to its atrophy; alternatively, the portal inflow into the left hemiliver increases, causing hypertrophy of the FLR.

This approach permits the performance of the scheduled hepatectomy (while concomitantly reducing the risk of fatal liver failure) in more than 50% of patients who were otherwise unresectable due to a small FLR.

Concerns regarding the comparative effectiveness of PVE versus PVL have been raised by certain authors. In an animal model, Furrer et al. revealed that the hypertrophy of the left hemiliver significantly increased following PVL versus PVE. These authors hypothesized that the entrapment of a greater number of macrophages in the embolized liver (due to the foreign-body reaction that is induced by the material used for embolization) explains this result [23]. Their conclusion that PVL is superior to PVE in inducing a regenerative response of the remnant liver is in contrast to that of Wilms et al., who stated that although PVL and PVE both induce liver hypertrophy, PVE is the most effective technique to increase the FLR [24]. These authors stated that PVE-induced vascular occlusion is more durable than that induced by PVL. Furthermore, the cause of the inferior regeneration in the ligation group was reported to be the formation of collaterals between the occluded and nonoccluded portions of the liver. To avoid this undesirable situation, certain authors recommended the transection and ethanol injection into the ligated portal branch [20]. Lastly, in addition to these experimental studies, a retrospective study of 35 patients revealed that PVL and PVE are similar in terms of both increasing the FLR and the conversion to resectability rate [25].

PVE- or PVL-induced liver hypertrophy involves both segments 2-3 and segment 4. Most patients that are subjected to PVL/PVE require a right trisectionectomy. In such patients, the principal objective of this maneuver is to increase the volume of segments 2-3 and not the volume of segment 4 (which is resected). To primarily increase the volume of the left lateral section, certain authors state that the optimum approach is to concomitantly occlude the right portal vein and the portal branches to segment 4 (right trisection portal vein embolization-R3PE) [26]. In 2000, Nagino et al. presented results that support this hypothesis, demonstrating that the volume gain of the left lateral section was higher in patients with R3PE relative to patients who received right portal vein embolization [26]. To date, we have performed R3PL in one patient, and the results were outstanding: the percent of FLR gain was 16.22%, whereas

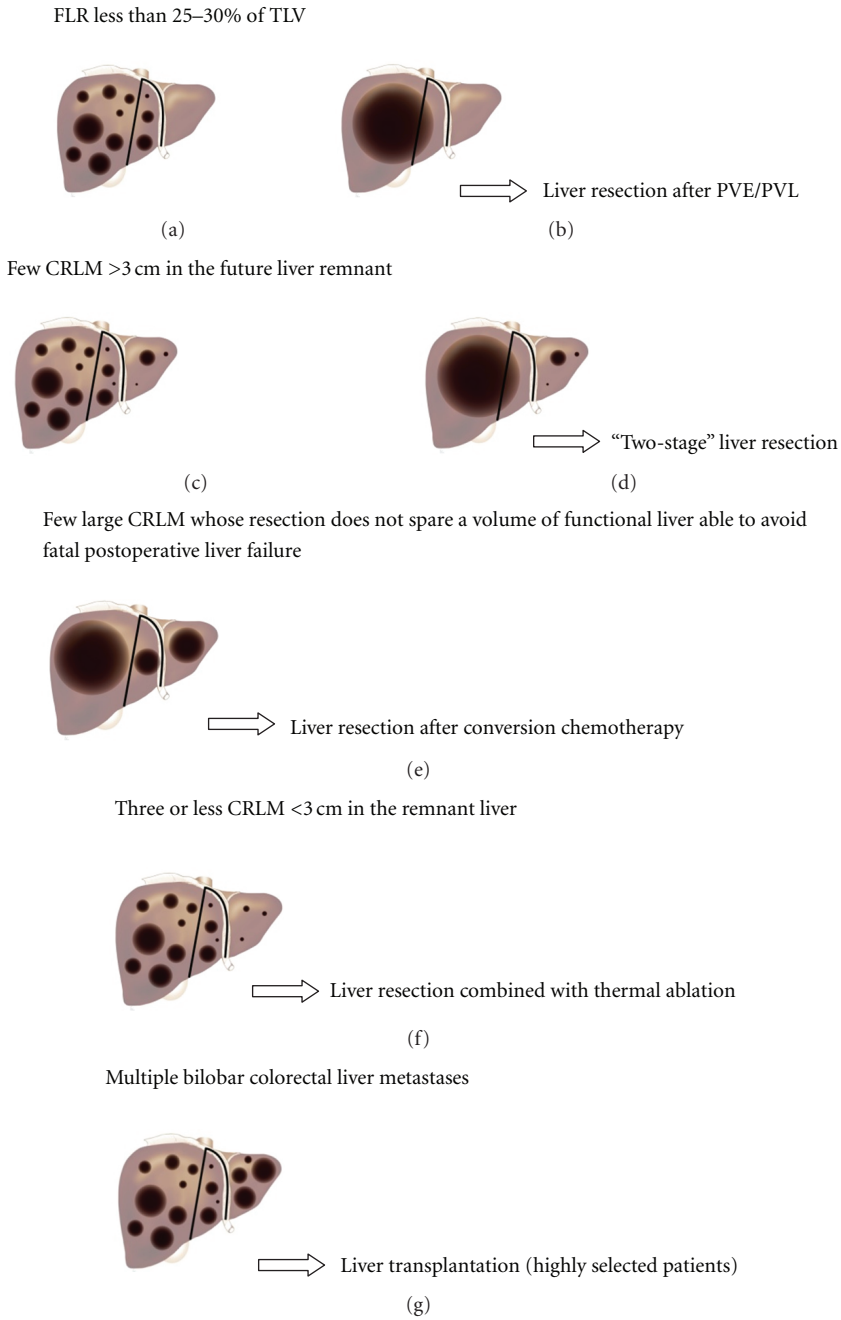

Figure 1: Strategies used for potentially curative treatment of the initially unresectable CRLM, depending on the location, number, and size of the lesions.

this metric was 10.8% in the patients who received a right portal branch ligation [27]. However, another study that was published in 2005 failed to confirm these results, revealing that the mean volume of segments 2-3 following embolization and the rate of the segments 2-3 volume increase were similar between the patients who received a R3PE and those that received a standard right portal vein embolization [7]. Therefore, definitive conclusions cannot be drawn regarding the usefulness of the embolization of the portal branches to segment 4, and further studies are required to clarify this subject. Most centers now prefer to routinely perform only right portal branch embolization/ligation in such patients.

To achieve a more marked and rapid hypertrophy of the FLR following portal vein ligation, Schnitzbauer et al. [28] and de Santibanes et al. [29] recently recommended the association of right portal vein ligation with "in situ liver transection/splitting". Using this approach, the authors achieved a significant and more rapid hypertrophy of the FLR, enabling subsequent curative liver resection during the same hospitalization. The authors concluded that this technique induces the rapid and more robust growth of the FLR [28] than is reported with portal vein occlusion alone. Moreover, this approach allows for the performance of a staged liver resection during a single hospital stay [29].

Two formulas can be used to calculate the percent of the FLR gain following PVE/PVL:

(a) (Volume of the FLR following PVE − Volume of the FLR prior to PVE) × 100/Volume of the FLR prior to PVE [30],

(b) %FLR following PVE −%FLR prior to PVE [12].

In a series of 30 patients, the percent of the FLR gain (calculated using the first formula) was 42% [10], whereas the FLR gain ranged from 9.7% to 13% in different series using the second formula [21, 27, 30]. In most patients, these percentages are generally sufficient to allow for a safe resection of liver metastases.

When PVE is planned, Bevacizumab should be used with caution given that Aussilhou et al. revealed the detrimental effect of this medication on the FLR gain; this effect is especially strong in patients who are older than 60 years and received more than six cycles [31]. However, other authors have demonstrated that this monoclonal antibody does not impair liver regeneration following PVE [32].

The most severe complications of right PVE are liver hematoma, liver abscess, thrombosis of the left portal vein, portal hypertension, and cholangitis. In a meta-analysis that was performed by Aboulkhir et al., the morbidity rate following PVE was 2.2%, and the mortality was zero [30].

The resectability rate following PVE/PVL in different centers ranges from 60% to 88% [10, 21, 22]. The primary reason of failure to perform the curative hepatectomy is not insufficient hypertrophy of the FLR but rather the progression of the disease. In our series, 5 of 13 patients (38%) exhibited disease progression following PVL, precluding a curative liver resection. The other 8 patients underwent successful complete resection of the initially unresectable CRLM. The resectability rate was therefore 62% [27].

The morbidity and mortality rates that were observed following curative hepatectomy were less than 35% and 4%, respectively, in most series [10, 22].

The 5-year survival rate of these patients was approximately 38% [10, 21].

It must be noted that in patients with liver metastases in the FLR, this approach is not recommended, due to the risk of rapid growth of these metastases. Such approach may jeopardize the chances of a subsequent potentially curative liver resection. Such patients should undergo a "two-stage" liver resection (see below) to clear the remnant liver prior to the PVE [33].

2.2. Two-Stage Liver Resection. The term "two-stage" liver resection has been used by a small number of authors to define a strategy that consists of a single liver resection that is performed following PVL and which does not include a sequential liver resection [20]. Herein, we shall use the nomenclature of "two-stage" liver resection for those procedures that consist of two consecutive hepatectomies.

This therapeutic strategy is used in patients with multiple bilobar CRLM, whose resection will not spare a sufficient amount of liver parenchyma to avoid postoperative liver failure. These patients usually require a right hepatectomy or a right trisectionectomy along with wedge resections of the metastases that are located in the left hemiliver or in the left lateral section (Figures 1(c) and 1(d)).

To avoid such extensive resections, which are accompanied by a high risk of postoperative fatal liver failure, it is recommended that a complete resection of the liver metastases be achieved in a two-stage surgical procedure. In the first stage, a limited resection of the metastases from the left hemiliver or the left lateral section (future liver remnant) is performed. In stage two (following the regeneration of the FLR), the bulk of the metastatic burden is resected by a right hepatectomy or trisectionectomy. FLR regeneration is essential to minimize the risks of hepatic failure following the second operation. Thus, PVE/PVL may be suitable in patients with small FLR to increase the safety of the second hepatectomy. To facilitate the second operation and to avoid disease progression between the first and the second intervention, it may be useful to deliver systemic or locoregional chemotherapy to shrink the metastatic bulk. To minimize the inhibitory effects of the chemotherapeutic drugs on liver regeneration, the chemotherapy should be begun three weeks following the first hepatectomy. This sequence is necessary, as liver regeneration is essential to the feasibility of the second resection [34].

Such a therapeutic approach is especially useful in patients with synchronous bilobar CRLM [35] given that (1) it avoids the cumulative risks of a simultaneous primary tumor resection and major hepatectomy, and (2) it allows for the evaluation of the chemosensitivity of the liver metastases and the guiding of the adjuvant therapy following the second operation. The resection of the primary tumor is performed in the first stage, along with a limited resection of the metastases from the future liver remnant (generally from the left hemiliver or the left lateral section). Occasionally, a right portal vein ligation is also performed during the first operation. Short-course chemotherapy (systemic or locoregional) should begin three weeks later. If the residual lesions will be stable or responsive to chemotherapy, the second liver resection should be performed.

The results of such an approach were first published by the Paul Brousse group in 2000. This group reported a resectability rate of 81% [34]. In other series, the resectability rate ranged from 66% to 75% [27, 33].

Among the published series, the morbidity rates following the first resection were less than 31%, and the mortality rates were zero [33, 34].

The morbidity rate following the second liver resection ranges from 45% to 56% [27, 33, 34]. Despite these relative high morbidity rates, the mortality was zero in most series [27, 33]. Nonetheless, a mortality rate of 15% following the second operation was reported by Adam et al. [34]. The authors explained that this result was a consequence of the combination of (1) the diminished tolerance of such patients to perioperative complications due to their advanced neoplastic disease and (2) the effects of the adjuvant procedures that were used to facilitate liver resection (chemotherapy, PVE).

The 3-year survival rates of these patients ranged from 35% to 54% [27, 33, 34], with a median survival of 44 months from the diagnosis of liver metastases [34].

In selected patients with multiple bilobar colorectal liver metastases, a "two-stage" liver resection could be avoided, by performing ultrasonically-guided hepatectomy.

2.3. One-Stage Ultrasonically Guided Liver Resection. The implementation of ultrasonography in liver surgery dramatically alters the approach to liver metastases, permitting a more accurate diagnosis and challenging the traditional paradigms of liver resection.

Intraoperative ultrasound (IOUS) allows for the detection of additional CRLM that were not revealed by preoperative imaging methods and is the most accurate technique for detecting liver tumors [36, 37]. However, standard IOUS may miss lesions that are smaller than 1 cm, especially in patients who are undergoing preoperative chemotherapy, whose CRLM exhibit a similar echo-pattern to that of the surrounding liver parenchyma. The use of contrast-enhanced IOUS (CE-IOUS) was demonstrated to improve the detection of CRLM and is the most sensitive and specific method for the diagnosis of CRLM [38].

In the mid 1980s, IOUS was first used to guide the puncture and balloon occlusion of the portal branch that feeds the portion of the liver to be resected, allowing for limited anatomical liver resections instead of major hepatectomies [39–41]. This technique decreased the risk of postoperative liver failure and was recommended principally in patients who have HCCs on liver cirrhosis.

In addition, IOUS offers a better estimation of the spatial relationships between the liver tumors and the intrahepatic vessels, permitting the resection of liver masses with the preservation of intrahepatic vascular structures even when the tumors are located in close proximity to major intrahepatic vessels. Furthermore, even when major hepatic vein(s) must be resected, color Doppler IOUS findings provide reliable information that may lead to the preservation of a portion of the liver parenchyma that is drained by those vein(s), avoiding major hepatectomies [42–45]. Thus, a novel liver resection technique was developed in recent years that is referred to as "ultrasonically guided hepatectomy". This technique opened the door to new procedures that allow for radical but conservative liver resections, reducing the requirement for major hepatic resections [46–48].

Because many patients exhibit colorectal liver metastases that are considered unresectable due to the insufficient remnant liver parenchyma following major hepatectomies, the use of this surgical technique (which spares a significant amount of functional liver parenchyma) allows for the complete resection of the metastases, reducing the risk of developing postoperative liver failure. Thus, this technique was used more frequently in patients with CRLM.

Moreover, ultrasonically guided liver resection decreases the requirement for major hepatectomies, obviating the requirement for portal vein occlusion prior to the liver resection and/or the necessity of a "two-stage" liver resection in selected patients.

In patients with CRLM that are located in close proximity to major hepatic veins or near the first-degree portal branches, a major hepatectomy is still the main surgical option at most centers. If the remnant liver volume following a major hepatectomy is critically small, a liver resection following portal vein occlusion, either by PVE or PVL, is generally recommended. In such instances, the patient is exposed to an interventional radiology procedure or a laparotomy prior to the curative liver resection. Each of these procedures presents additional risks of morbidity [30]. The development of the ultrasonically guided hepatectomy in recent years permits a more limited liver resection of poorly located CRLM, avoiding the necessity of a prehepatectomy PVE/PVL. In a series of 22 patients who presented poorly located liver tumors and who were scheduled for initial ultrasonically guided liver resection, a limited resection with or without hepatic vein preservation was achieved in 91% cases, providing lower morbidity rates than major resections following PVE and no mortality [43]. The rate of local recurrence (at the transection surface) was zero at a mean follow-up period of 23 months. Because this approach avoids portal vein occlusion (and its associated morbidity), the comfort of the patient is also improved. Moreover, the resectability rate following portal vein occlusion does not exceed 60–88%, due to either insufficient hypertrophy of the remnant liver or disease progression in the interval between the portal vein occlusion and the liver regeneration [21, 22, 49]. When an initial ultrasonically guided hepatectomy is performed, the risk of disease progression is avoided, and the hypertrophy of the FLR is no longer necessary. Thus, the resectability rate that is achieved by the ultrasonically guided approach appears to be higher than those that are achieved by PVE/PVL, broadening the indications for curative surgery in cases of CRLM [43].

In patients with multiple bilobar CRLM, the ultrasonically guided technique may also represent an effective alternative to the "two-stage" hepatectomy, permitting a curative and conservative liver resection [44]. The advantages of this approach over the "two-stage" liver resection are the comfort of the patient, a lower morbidity rate [44], and an increased possibility of repeat resections if the patient develops recurrent metastases [50–52]. Furthermore, the recurrence rate following one-stage ultrasonically guided liver resection was similar to that reported after "two-stage liver resection".

Due to the aforementioned benefits, the one-stage ultrasonically guided liver resection should be part of the armamentarium of the liver surgeon, especially in the context of patients with complex tumoral presentations.

2.4. Liver Resection Following Conversion Chemotherapy. This therapeutic strategy was first presented by the Paul Brousse group in 1996 [53] and is recommended in patients with a small number of large CRLM, the resection of which would not spare a sufficient amount of functional liver to prevent postoperative liver failure (Figure 1(e)). The goal of this approach is to "downsize" the liver metastases to an extent that allows for their complete resection. Therefore, a chance of a potentially curative liver resection is available to patients who otherwise may have only benefited from palliative treatment.

Until 20 years ago, the only efficient chemotherapeutic regimen that was used in patients with unresectable

CRLM consisted of 5-Fluorouracil (5-FU) and Folinic acid. Although this chemotherapy increases the overall survival rates and the progression-free survival rates of these patients, the response rates were less than 23%, and only anecdotal cases of liver metastases that shrink sufficiently to allow for a subsequent curative hepatectomy were reported [54–56].

The advent of new chemotherapeutic agents such as Oxaliplatin and Irinotecan led to significantly better results. The response rates that have been achieved by FOLFOX and FOLFIRI regimens range from 40% to 56% [57–59]. A strong correlation was observed between the response rates and the resection rates of patients with initially unresectable CLRM [60]. Therefore, more patients became resectable following so-called conversion chemotherapy. Folprecht et al. thus concluded that resectability should be considered a new endpoint for preoperative chemotherapy, focusing on the curative potential of this oncosurgical treatment [60].

The Paul-Brousse group published their updated results in 2004, reporting a 12.5% rate of conversion to resectability in 1104 patients with initially unresectable CRLM (following an average of 10 courses of chemotherapy) [14]. Apart from these very large series of patients, other centers have subsequently reported similar results in smaller numbers of selected patients who presented with initially unresectable CRLM that were rendered resectable by different chemotherapy regimens [61–63].

In many reports, the morbidity rates following hepatectomy in patients with initially unresectable CRLM [14, 62, 64] ranges from 23% to 28%, which are similar to those rates that are observed in patients with initially resectable CRLM. However, certain authors have reported significantly higher incidences of postoperative complications in patients who receive resections following "downsizing" chemotherapy, raising concerns regarding the deleterious effects of the preoperative chemotherapy on the liver parenchyma (see below) [65, 66]. The postoperative mortality rates are reported to be less than 2% in most centers, which are similar to those rates that have been achieved in patients who did not receive preoperative chemotherapy [14, 53, 62, 66].

The 5-year survival rate of patients who were rendered resectable by chemotherapy was 33% in the Paul Brousse group, a rate that was higher than those that were achieved by new palliative chemotherapeutic regimens in similar patients [14]. Although this survival rate is significantly lower than what can be achieved in patients with initially resectable CRLM (P value = 0.01), the 5-year disease-free survival rate of 22% that was reported in initially unresectable patients appears to fully justify the efforts to render to resectability, these patients with otherwise dismal prognosis [14].

The addition of targeted therapies (e.g., Bevacizumab, Cetuximab, and Panitumumab) to chemotherapy regimens may be useful in further increasing the rate of conversion to resectability in initially unresectable lesions. This hypothesis was confirmed in a series of patients whose liver metastases were refractory to previous rounds of conventional chemotherapy. The advent of Cetuximab to the next-line chemotherapy rendered 7% of these patients resectable, with morbidity and mortality rates of 50% and 3.7%, respectively, and a median survival of 20 months [67]. This study, similar to those of Zorzi et al., demonstrated that monoclonal antibodies in combination with conventional chemotherapy have no detrimental effects on the safety of liver resection [32]. Furthermore, Gruenberger et al. revealed that Bevacizumab has little detrimental impact on liver regeneration following hepatectomy [68]. However, it should be noted that the use of vascular endothelial growth factor inhibitors (e.g., Bevacizumab) prior to major surgery increases the risks of bleeding and wound healing complications [69]. This therapy should be discontinued 5–8 weeks prior to the surgical intervention [68, 70].

Several issues should be kept in mind when deciding to take this therapeutic approach.

(i) The response to chemotherapy cannot be assumed to persist. Metastases occasionally shrink and become resectable following several cycles of chemotherapy. However, if the chemotherapy is continued, the metastases may regrow and again become unresectable, closing the "window of opportunity" for a potentially curative hepatectomy [71]. Therefore, if the systemic disease is controlled, the liver resection should be scheduled as soon as the metastases become resectable.

(ii) If the chemotherapy is continued beyond the point when the metastases become resectable, it is possible the liver metastases will become smaller and will no longer be visible on imaging (CT/MR/PET scans). Such metastases are referred to as "vanishing metastases." Unfortunately, this "radiological complete response" or "clinical complete response" [72] does not indicate a cure, as a "pathologic complete response" is achieved in fewer than 20% of cases [73, 74]. In one-third of patients with radiological complete response, a laparotomy may reveal small metastases that were missed by the imaging methods or residual scars, the resection of which would reveal viable tumor cells. Alternatively, in patients without macroscopic residual tissue (on laparotomy) and negative (contrast-enhanced) intraoperative ultrasound, pathologic examination of the resected specimens, including liver segments where the metastases where initially located, revealed viable metastatic cells in 75% of cases [74, 75]. An indirect confirmation of the presence of viable tumor cells at the sites of the former metastases (which were invisible on laparotomy) is given by certain reports. In a series of patients with 31 CRLM that disappeared following chemotherapy and which were not observed on laparotomy, the resection of the initial metastases site was not performed. After a one-year follow-up, 23 (74%) metastases recurred in situ [74].

The survival benefit that is achieved by performing liver resection in patients with clinical complete response following chemotherapy was revealed by another study. Fourteen patients with radiological complete response following chemotherapy were not subjected to a liver resection, achieving a 5-year overall survival of 14% and a median survival of 30 months. In 25 patients who suffered from initially unresectable CRLM that were rendered to resectability by a FOLFOXIRI regimen and further resected, the 5-year survival rate was 43%, and the median survival was significantly higher (61 months, P value = 0.006) [62].

For these reasons, laparotomy is mandatory in patients with vanishing metastases, with the aim of resecting the macroscopic residual metastatic tissue or the sites of the initial CRLM ("blind resection").

The resection of the metastases sites is a very demanding operation, especially in patients with (initially) multiple metastases located deep in the liver. In such cases, computer-based virtual surgery planning is very useful, merging pre- and postchemotherapy computed tomography data. Recently, Oldhafer et al. presented such a surgical approach. Information that is processed using a computer is then intraoperatively transferred to the liver surface using an image-guided stereotactically navigated ultrasound dissector, enabling the surgeon to perform the resection [75].

In patients with initially multiple bilobar CRLM that become "invisible" following chemotherapy and that cannot be identified intraoperatively, it is frequently impossible to assume a complete resection of the metastatic sites. Thus, a small number of these "missing metastases" will remain. In such situations, Elias et al. recommended the placement of a chemotherapy catheter in the hepatic artery, allowing for a hepatic arterial infusion (HAI) with Oxaliplatin, along with systemic 5-FU and Folinic acid [76]. Using this approach, following a median follow-up period of 51 months, the missing metastases did not recur in 62% of the patients. The recurrence rate following HAI with Oxaliplatin was significantly lower than those that were noted in patients who were treated by systemic chemotherapy alone (P value = 0.01) [76].

Alternatively, it should be noted that a small number (4–15%) of CRLM that were treated by systemic chemotherapy prior to the liver resection achieved a complete pathologic response [72, 73, 77]. The complete pathologic response was observed both in patients with or without a radiologic complete response. The predictive factors for a complete pathologic response were age less than 60 years, maximum metastasis diameter of less than 3 cm, CEA levels at diagnosis below 30 ng/mL, an objective response following chemotherapy [72] and the use of hepatic arterial infusion chemotherapy [76]. The addition of Bevacizumab to the Oxaliplatin-based chemotherapeutic regimens did not appear to increase the incidence of the complete pathologic response (11.3% versus 11.6%; P value = 0.59) [78]. Patients with complete pathologic response achieved uncommonly high survival rates (76% at 5 years) [72].

(iii) Treatment with new chemotherapeutic drugs induces alterations of the nontumoral liver parenchyma, potentially impacting the results of the liver resection.

The initial belief was that use of Irinotecan may cause nonalcoholic fatty liver disease (NAFLD), which represents a spectrum of diseases. The mildest form of NAFLD is macrovesicular steatosis, and the most severe form is non-alcoholic steatohepatitis (NASH) [79]. Although a study that was published in 2003 revealed a correlation between prior treatment with chemotherapy and steatosis and highlighted the fact that morbidity rates following liver resections were significantly higher in patients with marked steatosis [80], more recent studies have reported differing results. In 2006, a multicenter trial revealed that Irinotecan was associated with steatohepatitis but not with steatosis [81]. Moreover, this latter study noted that the mortality rate was significantly higher in patients with steatohepatitis (14.7%) than in patients without steatohepatitis (1.6%, P value = 0.001).

The first study to reveal a correlation between Oxaliplatin and non-tumoral liver parenchyma injury was published in 2004 [82]. The results indicated that 78% of the patients who were preoperatively treated with Oxaliplatin exhibited sinusoidal alterations. These results were subsequently confirmed by other reports [83–85], which revealed that Oxaliplatin-based preoperative chemotherapy was associated with sinusoidal dilatation and congestion, peliosis, and venoocclusive disease. One of these studies reported that only long-course Oxaliplatin-based chemotherapy (6 or more cycles) is significantly associated with sinusoidal injury [85]. However, in a series that was presented by Vauthey et al., the risk of sinusoidal dilatation did not appear to increase with the duration of chemotherapy (although their patients received relatively short-course treatments) [81]. Interestingly, the addition of Bevacizumab to Oxaliplatin-based regimens appears to reduce the incidence and severity of hepatic injury [78]. The impact of these liver injuries on the clinical outcome of the patients who received resections following Oxaliplatin-based chemotherapy was assessed in several reports. None of these studies reported increased mortality rates following liver resection in patients with Oxaliplatin-related sinusoidal injury [79]. Two trials revealed that a limited course (fewer than 6 cycles) of Oxaliplatin-based therapy was not associated with increased morbidity rates following liver resection [81, 86]. However, Karoui et al. observed a statistically higher incidence of postoperative complications in patients who underwent a major hepatectomy following preoperative chemotherapy when compared with the patients who were subjected to a similar liver resection without preoperative chemotherapy [66]. Similarly, Nakano et al. observed that sinusoidal injury was significantly associated with increased morbidity and longer hospital stays in patients who underwent a major hepatectomy [85].

The above-mentioned pitfalls that are associated with preoperative chemotherapy justify the scheduling of the liver resection as soon as the metastases become resectable.

2.5. Liver Resection Combined with Thermal Ablation for Unresectable CRLM. This type of approach is especially recommended in patients with multiple bilobar CRLM who present with fewer than 3 liver metastases in the FLR, with each of these metastases being less than 3 cm in maximum diameter (Figure 1(f)). Another indication for this approach is when one or a small number of metastases are anatomically poorly located (e.g., in close proximity to the confluence of the three hepatic veins and the inferior vena cava or at the bifurcation of the portal vein) [87].

The operation consists of the resection of the main tumor bulk (generally by a right trisectionectomy) and thermal ablation of the unresected metastases from the remnant liver (frequently the left lateral section) [88].

This approach could be performed in a "two-stage" manner in patients with synchronous unresectable CRLM,

as described by Lygidakis et al. [89]. In the first stage, the following procedures are performed: (1) the resection of the primary colorectal tumor, (2) the ligation and transection of the relevant (right or left) primary portal branch, (3) the ablation of the metastatic nodules in the contralateral hemiliver, and (4) the insertion of an arterial catheter into the hepatic artery for locoregional chemo(immuno)therapy. The second stage of the operation consists of the resection of the tumoral liver (usually by right hemihepatectomy or trisectionectomy).

Thermal ablation can be achieved using radiofrequencies, microwaves, lasers, or cryotherapy.

To increase the chances of a complete hyperthermic ablation, the Pringle maneuver can be performed during the ablation [88].

The morbidity and mortality rates (44% and 2.3%, resp.) [27, 90] of patients undergoing combined liver resection and thermal ablation of unresectable CRLM appear to be similar to those of patients with initially unresectable CRLM that are rendered resectable by other therapeutic strategies.

A retrospective study that was published in 2004 reported a significantly higher local recurrence rate following resection combined with RFA (5%) than was observed following complete resection of the CRLM (2%). However, the patients were not stratified according to the maximum diameter of the ablated CRLM in this study [90]. It was recently demonstrated that the best results achieved by thermoablation are observed in patients whose CRLM were less than 3 cm in maximum diameter. Thus, a significantly higher rate (P value = 0.0001) of sustained complete ablation was achieved in patients whose lesions were less than 3 cm (66.7%) than for the patients with metastases that were larger than 3 cm (33.3%) [91]. One retrospective study (including resectable and unresectable CRLM) revealed that the local recurrence rate following the radiofrequency ablation (RFA) of metastases that were less than 3 cm in maximum diameter was 1.3% after a follow-up period of 33 months [92]. Moreover, another retrospective study (including patients with single CRLM treated by RFA or liver resection) determined that the 5-year overall and local recurrence-free survival rates were similar for patients with CRLM that were smaller than 3 cm who were treated either with RFA or liver resection [87].

However, in patients with multiple bilobar CRLM who are treated with a combination of RFA and liver resection, the overall and disease-free survival rates were significantly lower than for patients who underwent a complete resection of CRLM but significantly higher than in the patients who were treated by chemotherapy alone [90]. Moreover, Rivoire et al. revealed in a study of 57 patients with initially unresectable CRLM that the overall survival rates were similar for patients who underwent a complete liver resection following conversion chemotherapy and those who received liver resection combined with cryotherapy [93].

These results justify liver resection combined with thermal ablation of initially unresectable CRLM in patients who fulfill the above-mentioned criteria.

However, due to the lower recurrence rates achieved by the ultrasonically guided liver resection technique, this approach may be more suitable than liver resection combined with thermal ablation.

2.6. Liver Transplantation—A Future Opportunity? Unfortunately, there are still many patients with multiple bilobar colorectal cancer liver metastases who are not amenable to complete resection by any of the above-mentioned therapeutic strategies. In such patients, the only chance of complete removal of the liver metastases is total hepatectomy followed by liver transplantation (Figure 1(g)).

This approach was used in the early period of liver transplantation, achieving 1- and 5-year overall survival rates of 62% and 18%, respectively [94].

Due to organ shortages, it was considered that the allocation of an organ to a patient with such a short life expectancy following the transplantation was not ethically acceptable.

Currently, unresectable CRLM are considered to be a contraindication to liver transplantation.

However, the above-mentioned survival rates appear to be higher than those that can be achieved by palliative treatment, suggesting that even using the therapeutic options that were available thirty years ago, liver transplantation offered a higher survival benefit than the best palliative treatment that is currently available. Furthermore, due to recent progress in the fields of posttransplant immunosuppression and medical oncology and due to the more refined methods that are used in selecting patients to receive tailored therapies (based on reliable pathologic and biologic markers), improved survival rates could be achieved for selected patients who undergo liver transplantation.

Moreover, the ethical issues could be challenged by the use of a living donor liver transplantation given that, in such instances, the willing donation is directed toward a certain patient and not to the community [95]. Meanwhile, it is also considered unethical to offer a marginal graft to a patient with a good chance of long-term survival following liver transplantation. Because the number of available marginal grafts has increased in recent years, it may be acceptable to allocate such organs in selected patients with CRLM, at least in the setting of controlled trials.

Although the available data do not support liver transplantation as a routine procedure in patients with CRLM, we believe that a discussion of the current advances in this field and of the recently published results is worthwhile and should encourage debate on this issue.

By reviewing the largest series of patients undergoing liver transplantation for unresectable CRLM [96], it was revealed that 66% of patients with histologically negative lymph nodes were genetically positive for micrometastases when mutant allele-specific amplification (MASA) method was used to search for micrometastases in DNA from the regional lymph nodes of the primary colorectal cancer [97]. Those patients who were both genetically and histologically negative exhibited a significantly longer overall survival (P value = 0.011) than the other patients. Thus, Kappel et al. concluded that the genetic detection of micrometastases by MASA may be a powerful prognostic indicator for selecting

patients with colorectal liver metastases who could benefit from liver transplantation [97].

Over the previous two decades, certain further developments have emerged that may improve patient selection and the results of liver transplantation. For example, the advent of MDCT, gadolinium-enhanced MRI, and PET/CT scans has improved the detection of extrahepatic metastases, permitting the better selection of patients with colorectal cancer that had metastasized only to the liver. Recent studies have identified several biological parameters (such as the expression of p53, thymidylate synthase, Ki-67, K-ras, and human telomerase reverse transcriptase, as well as the type, density, and location of immune cells within the tumor) that may be more sensitive predictors of outcome in patients with CRLM than are the current histopathological methods that are used to stage colorectal cancer [98, 99]. Using a panel that incorporates these parameters, it may be possible to identify a highly selected group of patients who could greatly benefit from liver transplantation. Moreover, it has been hypothesized that the progress in posttransplant immunosuppressive therapy may decrease recurrence rates and improve the survival of patients who undergo liver transplantation for malignant disease, primarily due to the use of m-TOR inhibitors. Such immunosuppressive agents (sirolimus, temsirolimus) inhibit tumor growth and proliferation and exhibit antiangiogenic effects. These effects are in contrast to traditional immunosuppressive drugs, which appear to promote malignant cell proliferation [100, 101].

Over the past several years, taking into account the better expertise of transplant surgeons and the above-mentioned progress in both the selection of patients with CRLM and in the efficacy of posttransplant immunosuppressive regimens, certain authors have argued that the outcome of selected patients who undergo liver transplantation for unresectable liver metastases from colorectal cancer may be significantly improved [102]. For these reasons, certain authors have proposed a rational revisitation of the concept of liver transplantation in such patients. Thus, a pilot study (SECA-study) that aims to assess the survival and quality of life in patients receiving pretransplant chemotherapy, liver transplantation for unresectable CRLM, and posttransplant Sirolimus-based immunosuppressive regimen began in Norway in November 2006. The preliminary data of this study reveal a 94% survival rate after a median 25 months of postoperative follow-up and an excellent quality of life [102]. However, only 40% of these patients are disease-free after a median follow-up period of 25 months.

Favorable results were also recently reported in two patients with CRLM who were treated with liver resection followed by hepatic artery infusion chemotherapy and who underwent a liver transplantation for intraarterial chemotherapy-induced sclerosing cholangitis. The two patients were disease-free at 2 and 5 years following transplantation, respectively.

Based on these disparate results, definitive conclusions cannot be drawn; however, due to ethical considerations (i.e., organ shortage), liver transplantation with grafts from brain-dead donors cannot be accepted until 5-year survival rates exceed 50% [102].

However, if the results that are achieved by liver transplantation will become significantly higher than those can be achieved by nonsurgical therapies, it may eventually be difficult, in the future, to defend the prohibition of living-donor liver transplantation or liver transplantation with marginal grafts in highly selected patients with unresectable CRLM. Such a position would be difficult given that ethical considerations would no longer be valid in such situations.

3. Conclusions

Selected patients with initially unresectable CRLM may be rendered resectable following portal vein embolization or ligation, resulting in an important survival benefit or even a cure.

"Two-stage" hepatectomies (with/without PVE/PVL) may be performed safely, achieving complete resection of liver metastases and long-term survival.

The use of ultrasonographically guided hepatectomies decreases the requirement for major hepatectomies, portal vein occlusion and "two-stage" liver resections in patients with CRLM that are close to the hepatocaval confluence or in cases of multiple bilobar disease. This approach provides (1) an improved comfort and safety profile over "two-stage" liver resections and major hepatectomies following PVE/PVL and (2) a similar oncological benefit to other strategies.

Liver resection following conversion chemotherapy in previously unresectable patients may offer a considerable survival benefit. RFA could be combined with liver resection to increase the number of patients who are eligible for complete removal and ablation of CRLM.

In the future, highly selected patients with unresectable CRLM and favorable prognostic factors who receive liver transplantations with grafts from marginal donors or from living donors could achieve better survival rates than would be possible with palliative treatment. However, further studies and perioperative treatment improvements are required before this procedure achieves social acceptance.

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Clinical Study

Initial Experiences of Simultaneous Laparoscopic Resection of Colorectal Cancer and Liver Metastases

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Introduction. Simultaneous resection of primary colorectal carcinoma (CRC) and synchronous liver metastases (SLMs) is subject of debate with respect to morbidity in comparison to staged resection. The aim of this study was to evaluate our initial experience with this approach. *Methods*. Five patients with primary CRC and a clinical diagnosis of SLM underwent combined laparoscopic colorectal and liver surgery. Patient and tumor characteristics, operative variables, and postoperative outcomes were evaluated retrospectively. *Results*. The primary tumor was located in the colon in two patients and in the rectum in three patients. The SLM was solitary in four patients and multiple in the remaining patient. Surgical approach was total laparoscopic (2 patients) or hand-assisted laparoscopic (3 patients). The midline umbilical or transverse suprapubic incision created for the hand port and/or extraction of the specimen varied between 5 and 10 cm. Median operation time was 303 (range 151–384) minutes with a total blood loss of 700 (range 200–850) mL. Postoperative hospital stay was 5, 5, 9, 14, and 30 days. An R0 resection was achieved in all patients. *Conclusions*. From this initial single-center experience, simultaneous laparoscopic colorectal and liver resection appears to be feasible in selected patients with CRC and SLM, with satisfying short-term results.

1. Introduction

The liver is the most common site of hematogenous spread of primary colorectal carcinoma (CRC) [1, 2] and is affected in approximately 10–25% of patients having surgery [3]. Surgical resection is the most effective and potential curative therapy for metastatic CRC to the liver. The treatment strategies and outcomes for these patients have undergone many evolutionary changes [4–6]. Technical innovations in the field of surgery continue to evolve. Minimally invasive laparoscopic surgery improves postoperative recovery, diminishes postoperative pain, reduces wound infections, shortens hospitalization, propagates rapid return to full activity, and yields superior cosmetic results, without compromising oncological outcome [7, 8]. Currently, laparoscopic resection of primary CRC is performed in more than 40% of all patients in The Netherlands according to the Dutch Surgical Colorectal Audit [9]. However, the use of laparoscopy in liver surgery is still limited in The Netherlands [10].

There are several treatment options for CRC patients presenting with synchronous liver metastases (SLMs) depending on primary tumor location (rectum or colon) and extent of hepatic disease. Planning of perioperative treatment and type of surgery are discussed in a multidisciplinary team. Performing a simultaneous or staged resection of the primary tumor and liver metastasis is one of the items being discussed. Recently, a systematic review showed that combined resection resulted in shorter hospitalization and fewer complications in comparison with staged resection although a tendency was seen towards a higher postoperative mortality after simultaneous resection [11]. In contrast to the extensive literature on staged laparoscopic colorectal and laparoscopic liver surgery, there are only a few reports on combined laparoscopic colorectal and liver resection. The aim of this study is therefore to evaluate our initial experiences of simultaneous laparoscopic resection of primary CRC and SLM.

2. Materials and Methods

Five patients with primary CRC and a clinical diagnosis of SLM underwent combined laparoscopic colorectal and

liver surgery between March 2011 and January 2012 in the Academic Medical Center, Amsterdam. Patients charts and operative notes were reviewed retrospectively for the present study. Patient and tumor characteristics, operative variables, and postoperative outcome were evaluated.

2.1. Combined Modality Treatment of SLM. Treatment decisions in patients with CRC and SLM were based on location and complexity of resection of the primary tumor, extent of liver resection, feasibility of a laparoscopic approach, and physical condition of the patient. The institutional protocol of the Academic Medical Center indicates that simultaneous resection is preferred in patients who require minor liver resection (<3 segments) independent of primary tumor location. Neoadjuvant treatment preceding simultaneous resection is given for rectal primaries, consisting of short-course radiotherapy (5 × 5 Gy) followed by 3 to 6 courses of systemic chemotherapy (capecitabine and oxaliplatin). If major hepatectomy is indicated, a "liver first approach" is preferred with neoadjuvant treatment consisting of 3 to 6 courses of systemic chemotherapy which is preceded by short-course radiotherapy in case of a rectal primary. Systemic chemotherapy is completed in the adjuvant setting to a total number of 8 courses in patients with adequate clinical condition. All patients are discussed by the multidisciplinary team, and treatment is tailored to the individual patient with well-documented arguments for not following the institutional protocol (i.e., simultaneous right hemihepatectomy with right hemicolectomy in a fit young patient).

2.2. Surgery. Laparoscopic colorectal surgery was performed using a medial to lateral approach with intracorporeal dissection and vascular control. For right hemicolectomy, a vertical umbilical incision was performed for specimen extraction and extracorporeal anastomosis. A Pfannenstiel incision was used for specimen extraction in left-sided resections followed by an intracorporeal anastomosis using the double-stapling technique with circular stapler. The specimen was extracted through the perineum after laparoscopic abdominoperineal excision. Complete laparoscopic liver resection was performed with the surgeon in between the patient's legs. For metastasectomy in segments 7 and 8, a hand-assisted laparoscopic approach was performed with the surgeon standing at the left side of the patient. Total laparoscopic liver resection was started with insertion of a 10 mm trocar at the umbilicus followed by insufflation. For tumorectomy, two 5 mm trocars were positioned in the right and left upper abdomen. For left lateral sectionectomy, two 10/12 trocars were placed in each upper quadrant and an additional 5 mm trocar left subcostally. For tumorectomy in segments 7 and 8, a hand port was placed via a vertical umbilical incision followed by a 10/12 mm trocar in the right lower quadrant and a 5 mm trocar in the midline above the hand port. In one patient, an additional 5 mm trocar was placed right subcostally. The placement of trocars is shown in Figure 1. Parenchymal transection was performed by using an ultrasonic dissection device with additional haemostasis using bipolar diathermy. The left segmental (2/3) portal pedicle and left hepatic vein were transected using a laparoscopic 60 mm stapler in case of left lateral sectionectomy. The entire liver was systematically examined to identify occult lesions using laparoscopic ultrasound. The liver specimen was put in a plastic bag in case of total laparoscopic resection and extracted via the umbilical or Pfannenstiel incision.

3. Results

Four men and one woman with a pathological diagnosis of CRC and clinical or pathological diagnosis of SLM were included. The median age was 72 (range 56–77) years. Characteristics of each patient are displayed in Table 1. The average body mass index was 29.0 (range 23.9–30.1) kg/m^2. One patient (number 5) underwent laparoscopic resection of right-sided renal cell carcinoma two months earlier. During laparoscopy, a liver lesion was found and subsequent PET scanning and endoscopy revealed an additional sigmoid tumor. Preoperative treatment of rectal cancer consisted of short-course radiotherapy (5 fractions of 5 Gy) followed by three to four courses of systemic chemotherapy (oxaliplatin and capecitabine). All laparoscopic resections were successful without conversion to open surgery. Surgical outcomes are depicted in Table 2. The following procedures were performed: total laparoscopic right hemicolectomy with tumorectomy of segment 2 (extraction via umbilical incision), total laparoscopic sigmoid resection with tumorectomy of segment 4/5 including the gallbladder and tumorectomy of segment 3 (extraction via Pfannenstiel), assisted laparoscopic low anterior resection and diverting ileostomy with total laparoscopic left lateral sectionectomy (extraction via Pfannenstiel), and two laparoscopic intersphincteric abdominoperineal excision with hand-assisted laparoscopic tumorectomy of segment 7 and segment 8, respectively (extraction via the umbilical hand port). The incision created for hand port and/or extraction of the specimen varied between 5 and 10 cm.

Median operation time was 303 minutes (range 151–384) with an estimated total blood loss of 700 mL (range 200–850). Intraoperative complications consisted of a small perforation of the right hepatic vein during liver mobilisation in one patient, which was sutured using an additional 5 mm trocar. One patient had surgery-related complications with perineal wound infection and delayed gastric emptying (patient number 3). Other complications consisted of postoperative myocardial infarction necessitating reanimation and angioplasty (patient number 1), and pneumonia with delirium managed by intravenous antibiotics and haloperidol (patient number 2). Median postoperative hospital stay was 9 days (range 5–30). There was no postoperative mortality. An R0 resection of the primary tumor and liver lesions was achieved in all patients. Details of the pathological examination are displayed in Table 3. Definitive pathology of the liver in the patient with renal cell carcinoma and sigmoid carcinoma showed an adenocarcinoma originating from the upper gastrointestinal tract. At present, the origin of this

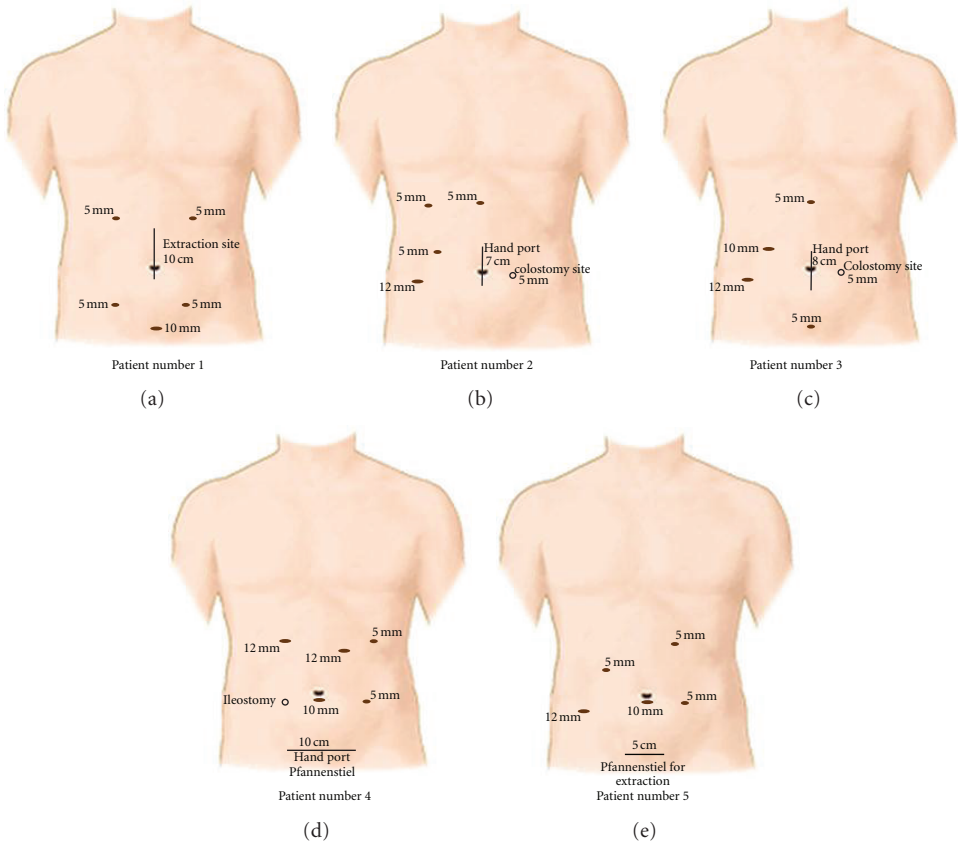

Figure 1: For simultaneous laparoscopic resection of colorectal cancer and liver metastases, a 10 mm subumbilical trocar was placed for pneumoperitoneum. An umbilical midline incision was created for specimen extraction in the patient that underwent a right hemicolectomy (patient number 1). In two patients, this vertical incision was used for the handport (patient numbers 2 and 3). For left-sided resections, a Pfannenstiel incision was used for specimen extraction. Four 5/12 mm trocars were positioned in the four quadrants for dissection. An extra 5 or 10 mm trocar was placed in the midline above the hand port for tumorectomy in segments 7 and 8. In one patient, an additional 5 mm trocar was placed right subcostal (patient number 2).

third primary tumor is unknown and this patient receives palliative chemotherapy because of progressive liver disease. In two of the three patients who already had induction chemotherapy, systemic treatment was continued postoperatively. The patient with myocardial infarction did not receive any (neo)adjuvant systemic chemotherapy because of his poor physical condition.

4. Discussion

The advantages of performing laparoscopic colorectal [7] or hepatic resections [8] by experienced surgeons have led to a prominent increase for these operative approaches in recent years. Separately for primary CRC and CRC liver metastases, laparoscopic resection has been shown to result in enhanced recovery and reduced morbidity with similar oncological outcome [7, 8]. This suggests that a laparoscopic combined approach will also benefit patients who are candidates for simultaneous resection. Open resection of both primary tumor and synchronous liver metastases often requires an extensive incision, especially if the location of the liver metastasis is opposite to the primary tumor location (i.e., right liver lobe and rectum). Using a laparoscopic approach, exposure can be improved due to a magnified visualization from different angles, even in the narrow pelvis or not easily accessible places of the upper abdomen. The feasibility of a simultaneous laparoscopic approach has been demonstrated by our initial experience in five patients, and the results presented confirm findings from the limited literature on this topic (Table 4).

Patients with a solitary, peripherally located metastasis in segments 2–6 are the most ideal candidates for simultaneous laparoscopic resection. Two additional trocars can provide adequate access to the liver besides the standard trocar placement for the colorectal procedure. Both specimens can be extracted via a single incision. Two patients in this series were diagnosed with a peripheral lesion in the posterior segments 7 and 8, requiring full mobilization of the right liver. Both liver mobilization and parenchymal transection could be accomplished in these patients using an umbilical hand port. Others also described the use of a hand port placed in an upper midline incision for liver mobilization [12, 17]. If major hepatectomy is indicated, the midline

Table 1: Patient characteristics and preoperative data.

Patient number	Sex/age (year)	Medical history	Location CRC	Location SLM	Preoperative radiotherapy	Preoperative chemotherapy
1	M/75	Angina pectoris, paroxysmal atrial fibrillation, hypercholesterolemia, intermittent claudication, severe coronary artery disease	Ascending colon	Segment 2	No	No
2	M/77	Hypertension, appendectomy, inguinal hernia repair	Rectum	Segment 7	5 × 5 Gy	Oxaliplatin and capecitabine
3	M/72	Hypertension	Rectum	Segment 8	5 × 5 Gy	Oxaliplatin and capecitabine
4	M/56	None	Rectum	Segment 2/3	5 × 5 Gy	Oxaliplatin and capecitabine
5	V/64	Hypertension, intermittent claudication, hypothyroidism, hypercholesterolemia, resection renal cell carcinoma	Sigmoid	Segments 3, 4/5	No	No

Table 2: Surgical results.

Patient number	Operation	Incision (cm)/location	Operation time (min)	Blood loss (mL)	Postoperative hospital stay (d)
1	Right hemicolectomy with tumorectomy of segment 2	10/midline	151	200	30
2	Abdominoperineal excision with hand-assisted laparoscopic tumorectomy of segment 7	7/midline	310	700	9
3	Abdominoperineal excision with hand-assisted laparoscopic tumorectomy of segment 8	8/midline	384	850	14
4	Low anterior resection and diverting ileostomy with total laparoscopic left lateral sectionectomy	10/Pfannenstiel	189	800	5
5	Sigmoid resection with tumorectomy of segment 4/5 including gallbladder and tumorectomy of segment 3	5/Pfannenstiel	303	300	5

incision can subsequently be used for vascular control and parenchymal transection. But even total laparoscopic major hepatectomy in combination with colorectal resection has been shown to be feasible in three patients (Table 4) [23, 25]. This allows for a small Pfannenstiel incision to extract the specimens, which has been proven to result in the lowest incidence of incisional hernia [26].

Simultaneous resection in synchronously metastasized CRC is still controversial. There are no randomized controlled trials comparing simultaneous and staged resections and the existing comparative studies are obviously difficult to interpret due to selection bias. Theoretical arguments against simultaneous resection are the combination of a clean and contaminated procedure, and the impaired protein synthesis of the liver increasing the risk of infection and compromising anastomotic healing. Furthermore, venous congestion by Pringle maneuver may result in bowel edema. However, according to a systematic review based on 14 comparative studies, combined resection was associated with lower morbidity [11]. This led the authors to conclude that simultaneous resection can be undertaken in selected patients by surgeons specialized in both fields of colorectal and hepatobiliary surgeries. Patient selection and expertise are essential for this complex type of surgery, and the multidisciplinary team should decide on optimal timing within multimodality treatment schedules.

Life expectancy of patients with liver metastasis from colorectal origin has been increasing as a result of improvements in liver surgery and systemic chemotherapy. Repeat surgery for recurrent liver metastasis has been shown to have similar outcome compared with the first liver resection [27–29]. An initial laparoscopic approach reduces adhesion formation and facilitates repeat resection, which has also been shown to be beneficiary in patients who need subsequent liver transplantation in case of patients with HCC [30]. Given the improved oncological outcome, quality-of-life issues related to abdominal wall integrity and cosmesis become more important, underlining the potential benefits of laparoscopy.

In conclusion, our initial experience in combination with the previously published data indicate that simultaneous laparoscopic resection of primary CRC and synchronous liver metastases is feasible and advisable in selected patients, provided that appropriate expertise is available.

Table 3: Pathological examination.

Patient number	(y)pTN stage/radicality	Circumferential resection margin (mm)	Diameter SLM (cm)	Resection margin SLM (mm)
1	pT2N2/R0	—	1.5	>10
2	ypT3N0/R0	1.5	1.9	8
3	ypT0N1/R0	Not applicable (complete response)	0.6	8
4	ypT3N0/R0	>10	7.0	6
5	pT1N0/R0	—	2.7	3

Table 4: Case reports and small cohort series describing laparoscopic colorectal surgery in combination with liver surgery using different approaches. Indication was colorectal cancer except for Inagaki et al. [12] (diverticular disease with cystic liver tumor).

Author	Year	*N*	Liver resection		Time (min)	Blood loss (mL)	LOS (days)
			Laparoscopic assisted	Total laparoscopic			
Inagaki et al. [12]	2003	1	1 LH	0	331	930	16
Geiger et al. [13]	2006	1	0	1 LLS	330	600	4
Leung et al. [14]	2006	1	0	1 LLS	350	500	7
Vibert et al. [15]	2006	8	0	8	NR	NR	NR
Law et al. [16]	2008	4	0	4	NR	NR	NR
Kim et al. [17]	2008	3	2 S 1 T	0	362 (210–450)	300 (300-300)	10 (9–16)
Pessaux and Panaro [18]	2009	1	0	1T + RFA	NR	NR	NR
Bretagnol et al. [19]	2008	3	0	1 LLS 2 T	NR	NR	NR
Sasaki et al. [20]	2009	9	0	2 LLS 7 T	418 (215–520)	219 (32–745)	9 (7–26)
Akiyoshi et al. [21]	2009	3	3 T	0	372 (300–453)	45 (30–60)	16 (16–23)
Casaccia et al. [22]	2010	1	0	1 LLS	455	NR	12
Lee et al. [23]	2010	10*	0	6 LLS 5 T 1 S 1 RH	401 (230–620)	500 (60–1000)	10 (7–15)
Hayashi et al. [24]	2011	4	2	2	378 (270–575)	138 (40–330)	11 (7–14)
Tranchart et al. [25]	2011	2	0	1 LH 1 RH	310, 345	200, 200	4, 6

LOS: length of postoperative hospital stay, NR: not reported, LH: left hemihepatectomy, LLS: left lateral sectionectomy, T: tumorectomy, S: segmentectomy, RH: right hemihepatectomy, RFA: radio frequency ablation, *13 resections in 10 patients.

Conflict of Interests

There is no conflict of interests disclosure or declaration of funding sources.

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Clinical Study

Initial Experience in Single-Incision Transumbilical Laparoscopic Liver Resection: Indications, Potential Benefits, and Limitations

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Background. Single-incision transumbilical laparoscopic liver resection (SITLLR) has been recently described in limited series. We report our experience in SITLLR and discuss the future of this approach in terms of indications, potential benefits, and limitations, with a special reference to laparoscopic liver resection (LLR). *Patients and Methods*. Six patients underwent SITLLR. Indications were biliary cysts (3 cases), hydatid cysts (2), and colorectal liver metastasis (1). Procedures consisted in cysts unroofing, left lateral lobectomy, pericystectomy, and wedge resection. SITLLR was performed with 11 mm reusable trocar, 10 or 5 mm 30° scopes, 10 mm ultrasound probe, curved reusable instruments, and straight disposable bipolar shears. *Results*. Neither conversion to open surgery nor insertion of supplementary trocars was necessary. Median laparoscopic time was 105.5 minutes and median blood loss 275 mL. Median final umbilical scar length was 1.5 cm, and median length of stay was 4 days. No early or late complications occurred. *Conclusion*. SITLLR remains a challenging procedure. It is feasible in highly selected patients, requiring experience in hepatobiliary and laparoscopic surgery and skills in single-incision laparoscopy. Apart from cosmetic benefit, our experience and literature review did not show significant advantages if compared with multiport LLR, underlying that specific indications remain to be established.

1. Introduction

Since the first reports in the nineteen's [1, 2], laparoscopic liver resection (LLR) has now become a well-recognized and accepted procedure for treatment of liver tumors in selected cases. Currently, feasibility, safety, and clinical benefits of LLR have been clearly demonstrated for treatment of both benign [3] and malignant liver tumors [4]. Initially, LLR have been reserved to small lesions, located in anterior liver segments, at distance of major vascular and biliary structures, but, now, the feasibility and safety of LLR for tumors located posteriorly, centrally or requiring a major hepatic resection have been established [5]. A step forward, laparoscopic living donor hepatectomy, including left lobectomy for liver transplantation in children [6] and right hepatectomy for adult liver transplantation, has been proposed by specialized groups [7]. Single-incision transumbilical laparoscopy (SITL), firstly performed in 1992 [8], recently gained interest in general surgery. SITL represents the latest advance of the laparoscopic approach, aiming mainly to improve the cosmetic outcomes, while other potential advantages such as reduced postoperative pain, minimized operative trauma, and reduced hospital stay still need further investigations. SITL has been successfully reported for several abdominal interventions, including appendectomy, cholecystectomy, inguinal and ventral hernia, splenectomy, partial gastrectomy, and colectomy [9].

On the ground of both, the advances of multiport LLR techniques and the recent development of SITL, some surgeons reported the feasibility of single-incision transumbilical laparoscopic liver resection (SITLLR). Most reports concern clinical cases [10–20], while only few centers described series with more than 5 cases [21–28] (Table 1). Accordingly, the feasibility and beyond the potential advantages and disadvantages of this technique remain to be determined. We report herein our initial experience describing 6 patients who underwent SITLLR for benign and malignant liver lesions. We discuss the feasibility of this approach and its potential benefits and limitations, particularly compared with multiport LLR.

2. Patients and Methods

Between April 2010 and February 2012, 6 patients were submitted to SITLLR. Patients' characteristics and type of disease are represented in Table 2. The first 5 patients had no previous surgical history, whereas the patient 6 had a laparoscopic total mesorectal excision for a rectal cancer 6 months before. Surgical procedures consisted in biliary cysts unroofing (patients 1, 2, 3), left lateral lobectomy (patient 4), pericystectomy of segment 7 (patient 5), and wedge resection of segment 8 (patient 6). Preoperative work-up was performed by standard hematological and biochemical laboratory evaluations, including relevant tumor markers. All patients had preoperative liver imaging, using CT scan and/or MRI. Additionally, patient 6 had a whole body FDG-PET scan to exclude the presence of extrahepatic metastases.

2.1. Surgical Technique. The patient is placed under general anaesthesia in supine position and with the legs apart. The surgeon stands between the patient's legs and the camera-assistant to the patient's left. The original umbilical scar is incised and the fascia opened at 1 cm. A purse-string suture using 1 polydioxanone (PDS) is placed in the fascia, and an 11 mm reusable trocar is inserted inside. A 10 mm 30°, rigid and normal length scope (Karl-Storz Endoskope, Tuttlingen, Germany) is used. A curved reusable grasper (Karl-Storz Endoskope, Tuttlingen, Germany) (Figure 1(a)) is inserted at 10 o'clock position through a separate fascia opening outside the purse-string suture and without trocar. This instrument is maintained in the surgeon's nondominant hand, and it is never changed during the entire procedure.

2.1.1. Cyst Unroofing. The other instruments for the surgeon's dominant hand, like the curved reusable coagulating hook (Figure 1(b)), the curved reusable bipolar scissors (Figure 1(c)), and the curved reusable suction device, are changed during the different steps of SITLLR and inserted at 3 o'clock position inside the purse-string suture and besides the 11 mm trocar (Figure 2). The procedure starts with the exploration of the abdominal cavity and identification of the biliary cysts. The cystic domes are identified and incised enough to empty the cystic cavity. Thanks to this manoeuvre a nonconnection between the liver cysts and the biliary tree is evidenced. A meticulously complete excision of the cystic roof is performed. Thanks to the curves of the instruments, the classic working triangulation of laparoscopy is established inside the abdomen (Figure 3(a)), and surgeon is able to work in ergonomic position during the entire procedure (Figure 3(b)). The liver cyst cavities are finally checked for bleeding and left opened without omental patch.

2.1.2. Other SITLLR. A 6 mm reusable trocar is inserted at 2 o'clock position outside the purse-string suture, in order to accommodate a 5 mm 30°, rigid and longer scope. The flexible laparoscopic multifrequency linear probe is inserted in the 11 mm trocar (Figure 4), and the procedure starts with the exploration of the liver parenchyma through the intraoperative ultrasonography (IOUS), which permits to determine the transection line of the liver parenchyma. Then, the optical system is switched again into a 10 mm scope. A disposable straight bipolar shear (Ligasure V, New Haven, Covidien, CT, US) is inserted through the 6 mm trocar. The liver parenchyma is transected. An internal working triangulation is often created thanks to the curves of the grasper (Figure 5(a)), but an external conflict between the optical system and the handle of the straight bipolar shears is frequently evidenced (Figure 5(b)). If necessary, a straight 5 mm clip applier (Weck Hem-o-lock, Teleflex Medical, Sint-Stevens Woluwe, Belgium) is inserted through the 6 mm trocar.

2.1.3. End of the Procedure. A custom-made plastic bag is introduced in the abdomen through the 11 mm trocar, and the specimen is extracted transumbilically. The instruments and trocars are removed; the umbilical fascia is closed using absorbable sutures, taking care to close the separate openings for the curved grasper and for the 6 mm trocar.

3. Results

Neither conversion to open surgery nor insertion of supplementary trocars was necessary. Median total operative time (between skin incision and closure of the fascia) was 126 minutes (range: 89 to 185 min), and median laparoscopic time (between beginning of pneumoperitoneum and removal of the instruments and trocars) was 105.5 minutes (range: 71 to 160 min) (Table 3). Median total blood loss was 275 mL (range: 40 to 500 mL). No intraoperative complications occurred, excepting a major bleeding during the hydatid cyst pericystectomy (patient 5). Median final umbilical scar length was 15 mm (range: 14 to 20 mm). The patients' pain medication was kept low. No early complications were registered within the first postoperative month, and patients were discharged from the hospital between the postoperative day 3 and 5. Pathological evaluation confirmed the preoperative diagnoses of benign biliary cysts, the hydatid liver cysts, and colorectal liver metastasis; for this latter patient the margin of resection was 1 mm. After a median followup of 8 months (range: 3 to 25 months), no late complications related to recurrent disease or to the access-site were observed.

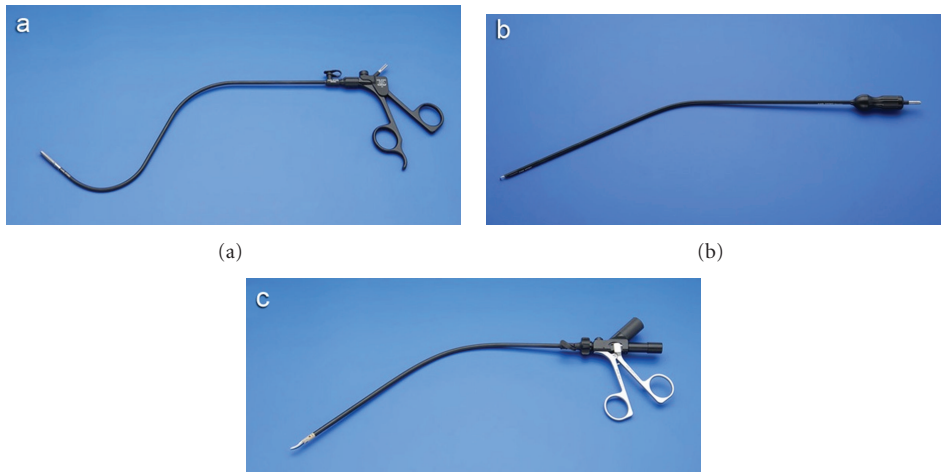
Table 1: Literature review for series of more than 5 cases.

Authors	Port	Instruments	Scope	Pathologies	Cases (n)	BMI (Kg/m^2)*	Operative time (min)*	Conversion (%)	Blood loss (mL)*	Final scar (cm)*	Hospital stay (days)*
Shetty et al. [24]	Gloveport (Sejong Medical)	Straight	5 mm Flexible	Malignant	24	NA	205#	8.3+ 16.6@	500#	5	8.5#
Cipriani et al. [23]	Triport (ACS), Quadriport (Olympus)	Straight	5 mm Flexible	Benign and Malignant	14	24.3	187	0+@	214	NA	5#
Zhao et al. [22]	Triport (ACS), 5-5-5 mm trocars	Straight and Articulating	5 mm Rigid and Flexible	Benign and Malignant	12	26.3	80.4	16.7+ 0@	45	2.5	4.3
Aikawa et al. [25]	SILS port (Covidien)	Straight	5 mm Flexible	Benign and Malignant	8	NA	148	0+@	2	3	6.2
Pan et al. [28]	10 mm and 5 mm trocars	Straight	10 mm	Benign and Malignant	8	26.2	89.7	0+@	64.3	2.5	3.7
Tan et al. [26]	various	Straight and Articulating	5 mm Flexible	Benign and Malignant	7	NA	142#	NA+ 0@	200#	NA	3#
Gaujoux et al. [21]	Gelport (Applied)	Straight	10 mm Flexible	Benign and Malignant	5	27.1	107	0+@	39	5	2
Cai et al. [27]	Triport (ASC)	Straight	10 mm Rigid	Benign	5	25.8#	87.3#	0+@	NA	NA	4.6#

*Mean.
#Median.
+Additional trocar.
@Open surgery.
NA: Not available.

Table 2: Patients' characteristics.

Patients	Age (years)	Sex	BMI (Kg/m^2)	Indication (liver segment)	Intervention
1	53	F	20.8	Biliary cyst (4, 7, 8)	Cyst unroofing
2	59	F	30.2	Biliary cyst (3, 4)	Cyst unroofing
3	46	F	20.5	Biliary cyst (4, 5, 6, 7)	Cyst unroofing
4	24	F	24.4	Hydatid cyst (2, 3)	Left lobectomy
5	26	F	20.6	Hydatid cyst (7)	Pericystectomy
6	65	F	23	Colorectal metastasis (8)	Wedge resection



(a) (b) (c)

Figure 1: Curved reusable instruments according to DAPRI: grasping forceps III (a), coagulating hook (b), bipolar scissors (c) (courtesy of Karl Storz-Endoskope, Tuttlingen, Germany).

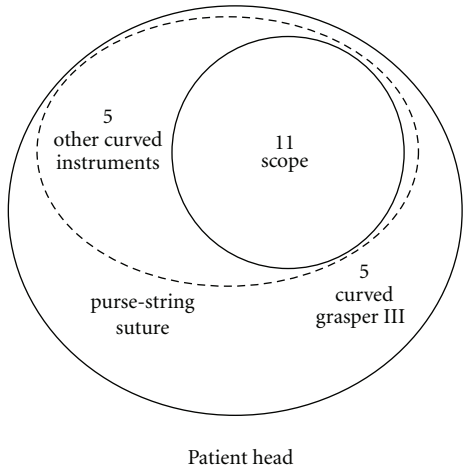


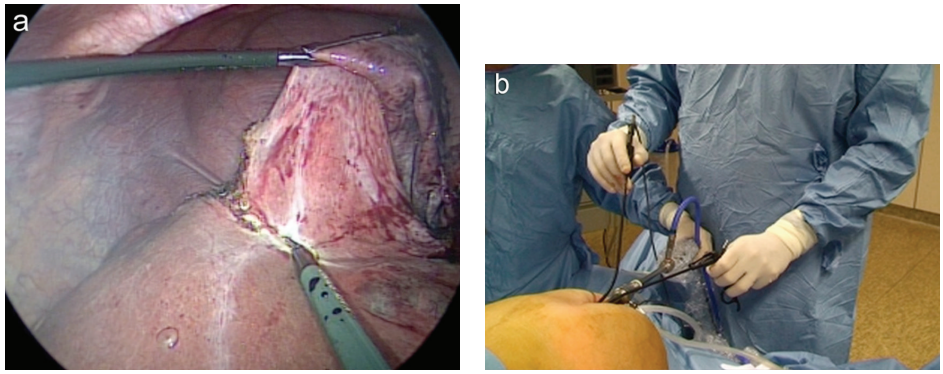
Figure 2: Umbilical access during cyst unroofing: placement of purse-string suture, 11 mm trocar for the 10 mm scope, and 5 mm curved instruments without trocars.

4. Discussion

The development of new techniques to reduce the surgical trauma and to minimize the abdominal wall damage is an obvious trend in liver surgery. Accordingly, LLR has been increasingly performed this last decade, becoming now a standardized procedure in selected cases, able to provide significant benefits as compared with classical open liver resections [29, 30]. SITLLR represents an ultimate evolution of the laparoscopic approach to the liver, being considered as very minimally invasive. The objective of SITLLR, beyond the cosmetic gain, is to further reduce the global surgical stress, potentially having a favorable impact on the postoperative evolution. At this point of the experience, several questions on SITLLR remain to be addressed, concerning the feasibility and mostly the reproducibility of this technique, the indications, selection criteria, limitations, effect on postoperative outcomes, and long-term results. It is on these bases that it would be possible to evaluate if SITLLR could become, more

Table 3: Operative and postoperative outcomes.

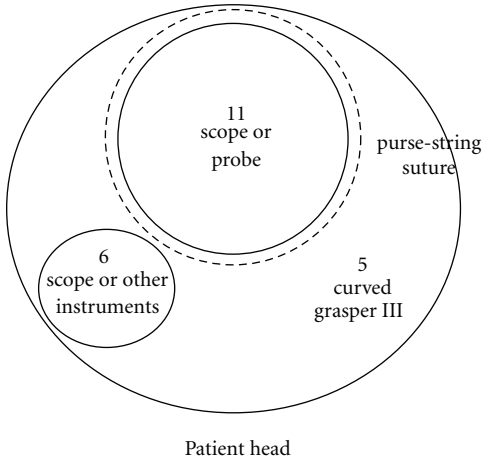
Patients	Total operative time (min)	Laparoscopic time (min)	Blood loss (mL)	Final scar length (mm)	Length of stay (days)	Followup (months)
1	90	81	50	14	3	25
2	89	71	40	14	3	13
3	138	115	400	16	4	3
4	114	96	350	20	5	9
5	185	160	500	16	5	7
6	158	140	200	15	4	6
MEDIAN	126	105.5	275	15	4	8



(a) (b)

Figure 3: Cyst unroofing: internal working triangulation (a) and external ergonomy (b) using curved reusable instruments.

than just a technical challenge, a real therapeutic option to improve the outcomes of patients submitted to liver resections. For such evaluation, the growing experience of SITLLR should be closely confronted to the well-established results of LLR, serving as standard of comparison. Several reports have reported the feasibility of SITLLR in selected cases [21–28]. Accordingly [21, 23, 25, 26, 28], our series confirms as SITLLR can be performed without conversion to open surgery or insertion of supplementary trocars, including also the resection of the lesions located in posterior liver segments. From a technical point of view, the objective during SITLLR is to maintain the procedure as similar as possible to the principles of multiport LLR. As a matter of fact, the technique described here is basically close to multiport laparoscopy, with the main difference that it is performed through the same umbilical incision, using instruments close to each other. One of the main rules of laparoscopy, which consists in maintaining the optical system as the bisector of the working triangulation [31], is respected during SITL because the 10 mm scope is maintained in the center of the umbilical access and the instrument for the surgeon's nondominant hand (curved grasper) on the right side of the access, whereas the instruments for the surgeon's dominant hand (coagulating hook, bipolar scissors, bipolar shears, clip applier, suction device) on the left side. The curved grasper is never changed during the entire procedure, whereas the instruments for the surgeon's dominant hand are continuously changed and replaced by the 5 mm scope during the step of IOUS. This step is the only one where one of the above laparoscopic rules is not respected, because the optical system is inserted laterally to give the place to accommodate the ultrasound probe. The technique described here, differently from the common SITL [9], did not increase the cost of standard laparoscopy, because all of the material implemented is reusable, except for the straight bipolar shears used during the parenchymal transection. As during multiport LLR, SITLLR parenchymal transection can be performed using several devices like Harmonic ACE (Ethicon Endosurgery, Cincinnati, OH, US) [21, 26, 28], saline-linked sealing dissector (SH2.0, TissueLink Medical's Dover, NH, US) (12), SonoSurg (Olympus, Tokyo, Japan) [14, 23], cavitron ultrasonic surgical aspirator (CUSA Excel, Valley Lab Inc., Boulder, CO, US) [24], Surgiwand (Covidien, Mansfield, MA, US) [24], Maryland type forceps and bipolar forceps combined with suction irrigation system [25], or Ligasure (Covidien New Haven, CT, US) [26, 28]. We adopted the use of curved coagulating hook and curved bipolar scissors for cystic dome resection and straight bipolar shears for parenchyma transection. Comparing these two instruments, surgeon was immediately confronted with the problem of external conflict between the optical system and the handle of the straight bipolar shears because, differently from the curved tools, both instruments are supported by a straight shaft (Figures 4 and 5). A significant gap was observed between the total and the laparoscopic times. This interval time can be explained by the need to get access to the peritoneal cavity as well as the time to meticulously close the umbilical access and the separate fascial openings at



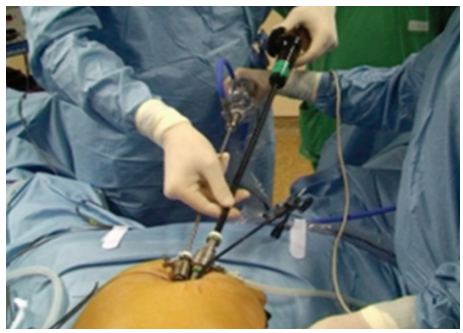
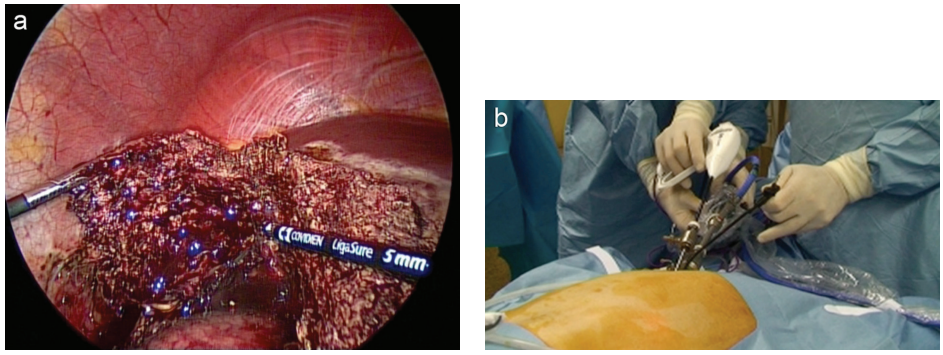


Figure 4: Umbilical access during other SITLLR: IOUS performed with the insertion of the ultrasound probe into the 11 mm trocar and use of long scope through the 6 mm trocar.

the end of the procedure, while laparoscopic time in this series remained similar to that previously reported [21]. This could be surely improved thanks to the surgeon's learning curve, and the time of laparoscopy could be reduced if particular devices with multiple functions like tissue division, hemostasis, irrigation, and suction are adopted [25]. Blood loss during SITLLR as well as during multiport LLR remains a factor related to the use of specific instruments for the parenchymal transection, to the extension of the parenchyma resected, to the time of transection, and, lastly, to the occurrence of intraoperative complications [21–25, 28]. In one case of this series (patient 5), a pericystectomy performed in segment 7 for a hydatid cyst, a significant bleeding was achieved, most probably in relation to the difficult access to superior and posterior liver segments and to the longer time needed for parenchymal transection. Still, no patients of the series necessitated blood transfusions, and no postoperative early complications were recorded.

After a median followup of 8 months, we did not achieve any complications related to the access site, to the remaining liver tissue, and to the general patient's conditions, but a longer followup is necessary for the evaluation of recurrent disease and for the appearance of incisional hernia at the access site. Thanks to the technique described here, the umbilical incision length is kept minimal. This result can be obtained because disposable port devices, requiring larger incision [9], are not used. Moreover, tumor's size and pathology are factors influencing the final scar length because malignant tumors superior to 30 mm of diameter need enlargement of the scar for extraction and intact specimen for pathological examination [14, 23, 26]. In our experience benign lesions, like biliary and hydatid cysts, were fragmented at the level of the umbilicus in a plastic bag, while malignant lesions were selected for SITLLR if small and with a diameter inferior to 3 cm [21, 22, 25]. In case of larger lesions, the final scar length has to be enlarged [23, 24, 26], sharing then an increased risk for development of incisional hernia [32, 33]. Such risk can also be associated to the placement of the final drain through the scar [10, 23]. As previously reported [21, 26], and similarly to our attitude during multiport LLR, we did not use a drain. In cases where a drain has to be left in the abdomen, we prefer to use a different abdominal wall punction, out of the umbilicus, in order to avoid the risk of incisional hernia. This punction can also be used during SITLLR to insert a needlescopic (3 mm) instrument [22] or a classic additional trocar [14, 23]. Hence, SITLLR becomes a technique of reduced port surgery, using two accesses, one at the umbilicus and one in another abdominal quadrant. Similarly, a supplementary instrument can also be inserted for technical problems due to tissue manipulation or compromised visualization [22] and noncontrolled perioperative bleeding or limited length of instruments [24]. Other factors of selection for SITLLR are the patient's body mass index and the patient's height, because it can be a cause of conversion to multiport laparoscopy [22, 24]. According to other authors [23, 26], we did not consider previous abdominal surgery, like in our patient 6, as a contraindication to SITLLR. Potential indications for LLR have now been clearly identified, showing essentially no predefined contraindications as compared with open liver resection in terms of disease pathology, including both benign and malignant tumors, either primary hepatocellular carcinoma or liver metastases. Importantly, with the reserves due to the absence of randomized trial and many selection biases, no oncological disadvantages have been shown for laparoscopic approach as compared with standard open procedure, neither in terms of radicality of resection nor for the risk of tumor cell seeding and long-term outcomes [34–38]. At this point of the experience, there are no reasons to consider that the same would be true for SITLLR. From surgeon's side, several statements clearly underlined that LLR should be performed by surgeons experienced in liver resections, meaning knowledge of hepatic anatomy, experience in open liver surgery, and skills in the use of IOUS [30]. Additionally, extensive experience in laparoscopic surgery and ability to identify and control major vascular and biliary structures laparoscopically are mandatory before embarking on multiport LLR [34]. Regarding the application of SITL to the liver, it is most probably reasonable to go back to the initial development of LLR, both in terms of indications and surgeon's experience. Accordingly, small anterior tumors, including malignant lesions, could be selected for SITL if the transection plane is well defined and at distance of the major biliary and vascular structures. Shetty et al. [24] described



(a) (b)

Figure 5: Other SITLLR: internal triangulation using straight disposable bipolar shears and curved reusable grasper (a), and external view (b).

a good indication for SITLLR in all the patients with well-localized lesions, whereas other authors focused on the importance of solitary tumors located on the anterolateral segments of the liver [25, 26, 28] or in the left liver lobe [21, 23] because the liver suspensory ligament helps for surgical-site exposure, and parenchymal division line remains in the same axis of the port site and instrumentations. Still, the specific technical problem created by the single caccess should not be underestimated, relying mainly on difficulties of exposure and on surgeon's and instruments' positions. Such ergonomic difficulties could lead to inadequate sections planes that could be a major concern for oncological indications, requiring safe but economic margins resection. Furthermore, other steps of SITLLR technique are limiting factors, like the frequent changes of the instruments for the surgeon's dominant hand and the use of IOUS through the single umbilical access. We agree with other authors [24] to consider limiting factors for SITLLR, patients with vascular involvement, extrahepatic disease, contraindication to laparoscopy, malignant lesions greater than 5 cm because the incision required to extract the specimen itself defeats the purpose of SITL. Other challenges in SITLLR remain technical difficulties related to massive liver dissection, access to the hilum for eventual Pringle maneuver, insertion of ultrasound probe through the single access, frequent alternation and adjustment of instruments, shifted division line, restriction by the length of the laparoscopic instrument, inappropriate placement of the drain, and control of bleeding during parenchymal dissection. Hence insertion of one or more trocars [22, 24] or conversion to open surgery [24] becomes strongly recommended. The following question relies on the identification of eventual intraoperative and early postoperative benefits of SITLLR as compared with multiport LLR. Regarding the results of LLR, even in the absence of randomized studies, several reports clearly indicated nowadays the advantages of this technique as compared with open liver resection, including less intraoperative blood losses, reduced requirements for blood transfusions [36–42], eventually associated with reduced postoperative complications rates and shorter hospital stays [38–40, 42, 43]. Short-term benefits of LLR, as compared with classical open liver resections, were strikingly observed in treatment of hepatocellular carcinoma in cirrhotic patients; in these cases, the avoidance of a subcostal incision interrupting venous portocaval shunts could be critical. Potential benefits of SITL, out of cosmetic outcomes, could be the postoperative pain, which has been considered one of the major outcome measures in the prospective randomized studies [44, 45], but a final sentence remains of concern. We achieved a non-additional use of pain medication used for LLR in this initial experience as reported [21–23, 26], allowing the patients to be discharged before the postoperative day 5. In conclusion, at this time SITLLR remains a challenging procedure. Feasibility has been reserved for highly selected cases, but it has to be performed by formed surgeons in hepatobiliary and laparoscopic surgery with skills in general SITL. Apart from its cosmetic benefits, the future of this technique will be dependent on the confirmation of significant results if compared with multiport LLR and, then, of objective advantages, such as a reduction of the global operative stress and/or an improvement of postoperative outcomes.

Conflict of Interests

G. Dapri is a consultant for Karl Storz-Endoskope (Tuttlingen, Germany). The other authors have no conflict of interests.

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Review Article

Laparoscopy in Liver Transplantation: The Future Has Arrived

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In the last two decades, laparoscopy has revolutionized the field of surgery. Many procedures previously performed with an open access are now routinely carried out with the laparoscopic approach. Several advantages are associated with laparoscopic surgery compared to open procedures: reduced pain due to smaller incisions and hemorrhaging, shorter hospital length of stay, and a lower incidence of wound infections. Liver transplantation (LT) brought a radical change in life expectancy of patients with hepatic end-stage disease. Today, LT represents the standard of care for more than fifty hepatic pathologies, with excellent results in terms of survival. Surely, with laparoscopy and LT being one of the most continuously evolving challenges in medicine, their recent combination has represented an astonishing scientific progress. The intent of the present paper is to underline the current role of diagnostic and therapeutic laparoscopy in patients waiting for LT, in the living donor LT and in LT recipients.

1. Introduction

In the last decades, laparoscopy has revolutionized the field of surgery. Video laparoscopy was officially born in 1987, when Professor Phillipe Mouret performed the first cholecystectomy in Lyons, France [1]. Many procedures previously performed with the open technique are now carried out with the laparoscopic approach. Several advantages are associated with laparoscopic surgery compared to open procedures: reduced pain due to smaller incisions and haemorrhaging, shorter hospital length of stay, and a lower incidence of wound infections are all arguments that gave strength to the widespread of laparoscopy.

Similarly, liver transplantation (LT) has radically changed the care for many patients with hepatic end-stage diseases. The first human LT was performed in 1963 by Professor Thomas Starzl [2] in Denver, United States: however, due to its initial poor results, LT remained an experimental therapy for several years. Only introduction of cyclosporine [3] markedly improved patient outcomes, turning LT to a standard clinical treatment for more than fifty adult and paediatric liver pathologies and, at the same time, allowing to achieve excellent results in terms of survival.

The intent of the present paper is to underline the current role of diagnostic and therapeutic laparoscopy in patients waiting for LT, in the living donor LT and in LT recipients.

2. Pretransplant Surgery

2.1. Laparoscopic Liver Resection. The first nonanatomical laparoscopic hepatectomy was performed by Gagner in 1992 [4] and the first anatomical one by Azagra in 1996 [5]. Since these first experiences, laparoscopic approach for hepatic resection has been adopted in different centres, showing its feasibility and safety in well-selected patients [6–10] and also confirming its prerogatives (shorter operative times, less bleeding) even in this very complex type of surgery [7, 11].

However, malignant tumors were initially considered a contraindication for mini-invasive approach. Only in the last years, this risk has been reconsidered, showing no difference in margin-free resection, port-site recurrence, or tumour seeding rates between open and laparoscopic techniques [12–15]. Consequently, malignant tumors do not represent anymore a contraindication for an expert surgeon in choosing a laparoscopic approach [16]. Until now, more

than 3,000 minimally invasive hepatic resections have been reported in the literature [17], and-small-to medium sized procedures have become commonplace in many centres [18].

Recently, a consensus conference [19] has underlined that acceptable indications for laparoscopic liver resection are (a) solitary lesions with a diameter ≤5 cm, located in segments II–VI; (b) laparoscopic approach to left lateral sectionectomy (LLS) should be considered as a standard practice; (c) although all types of liver resection can be run laparoscopically, major liver resections (e.g., right or left hepatectomies) should be reserved for experienced surgeons facile with more advanced laparoscopic hepatic resections.

The main indication for resection in patients waiting for LT is represented by hepatocellular carcinoma (HCC). Transplant surgeons are well aware that a LT after previous surgery could represent a real challenge, increasing technical difficulty caused by adhesions [20–22]. Basing on these considerations, laparoscopy as bridge to LT may reduce such problems [23].

Despite no prospective randomized controlled trials have been performed yet, some studies based on matched comparisons showed similar mortality and even lower morbidity rates after laparoscopy with respect to open liver resection. After laparoscopy, 3-year patient survival rates of 60–93% and 3-year disease-free survivals of 52–64% have been reported [8, 24–29].

Advent of robotic surgery has further improved the opportunity of mini-invasive treatment of HCC. The robotic approach may enable liver resection in patients with cirrhosis, allowing for technical refinements of laparoscopic liver resection due to 3-dimensional visualization of the operative field and instruments with wrist-type end-effectors [30–32].

2.2. Laparoscopic Radiofrequency Ablation. Radiofrequency (RF) ablation represents a nonsurgical locoregional treatment, used in very well-selected patients with nonresectable HCC waiting for LT. In the last years, laparoscopic or hand-assisted RF has shown promising necrosis and survival rates [33, 34], providing a substrate for their safe adoption [35]. The main advantage of laparoscopic RF with respect to percutaneous approach is the opportunity to detect pre-operatively undetectable lesions using an intraoperative ultrasound (IOUS) [36, 37]. IOUS remains the most sensitive imaging modality for HCC, being able to detect new lesions in 13.1% to 30% of cases [38–42]. In a study comparing laparoscopic liver resection and RF, Santambrogio et al. [43] identified 15 (20%) of 74 cases with previously undetected lesions in the RF group. Laparoscopic RF also consents to treat lesions considered inappropriate for percutaneous RF due to the high risk of injury in the diaphragm, stomach, or bowel [44–46]. Similarly, laparoscopic RF minimizes the risk of complications in patients previously operated in the upper abdominal quadrants [47].

2.3. Laparoscopic Kasai Procedure in Children with Biliary Atresia. Laparoscopic portoenterostomy, also named Kasai procedure, for biliary atresia was first reported by Esteves et al. in 2002 [48]. Besides its safety and feasibility, laparoscopic Kasai can provide the advantage of a lower hepatic adhesions rate, which ease the potential "salvage" LT. Martinez-Ferro et al. reported 41 cases of laparoscopic Kasai, with only one conversion [49], and encouraging results in terms of postoperative bile flow rates. However, the only prospective study comparing open and laparoscopic procedure was stopped after observing that laparoscopic patients showed a significantly shorter time between Kasai procedure and LT [50]. Therefore, the role of laparoscopic Kasai remains unclear [51], being reserved to paediatric centres with high specialization in minimally invasive surgery.

3. Laparoscopic Living Donor-Hepatectomy

The early idea of solid organ transplantation using living donors began with kidney transplants; similarly, laparoscopy for living donation was initially developed for kidney transplantation, with the intent to offer a less aggressive procedure to the donor. In fact, laparoscopic nephrectomy is associated with less postoperative pain, decreased length of hospital stay, faster return to normal activity, smaller scars, and less morbidity [52]. As a consequence, an increased number of kidney transplants using living donors have been recently observed in many centres [53, 54].

Living-donor liver transplantation is a complex procedure, with major risks of morbidity and mortality with respect to kidney donation: the reported mortality of this procedure has varied from 0.2% to 0.5% [55]. Clearly, donor risk increases according to the type of hepatectomy (LLS < left hepatectomy < right hepatectomy (RH)).

Typically, a LLS or a left hepatectomy is sufficient in a paediatric living liver donation, while a RH is necessary for an adult-to-adult donation.

However, despite different surgical approaches could be adopted, open living donation always requires a large abdominal incision. This aspect, combined with postoperative pain, long hospital stay, and long periods of recovery, represents a barrier to donation, especially in young women [56].

Recently, experimental model has demonstrated the feasibility of laparoscopic living donation using the available technology [57].

Concurrent improvement in laparoscopic surgery for hepatic tumours enhanced feasibility and safety of more complex procedures [18], leading to the establishment of laparoscopic surgery for liver living donors. Soubrane et al. [58] reflected on the quality of the graft and the morbidity rates in the donor: they reported comparable results in both conventional and laparoscopic techniques apart from longer operative times and lower blood losses in the laparoscopy group.

3.1. Paediatric Donation. Paediatric living donation provides similar or better short-term graft function and long-term survival rates with respect to postmortem donor LT: the first case of laparoscopic donation was reported by Cherqui et al. [56]. In 2006, Soubrane et al. [58] reported the safety of laparoscopic LLS in 16 consecutive live donors compared

with the conventional LLS. According to the first series experienced, the liver graft typically includes the LLS (i.e., segments II and III according to Couinaud's classification), left branch of hepatic artery, left portal branch, left bile duct, and left hepatic vein. After these initial experiences, several other new series have been reported worldwide [59, 60].

Recently, Kim et al. compared 11 laparoscopic LLS for living donation with 11 open ones, showing that the laparoscopic group had significantly shorter hospital stay, whilst duration of operation, blood loss, warm ischemia time, and out-of-pocket medical costs were comparable between groups [61].

A similar study from Washington DC compared 15 laparoscopic or laparoscopic-assisted left or right hepatectomies for liver donation with 15 hepatectomies with open access: no substantial differences were observed in terms of early graft function, allograft biliary, and vascular complications and survivals (1-year graft and patient survival: 100% versus 93% in laparoscopic and open group, resp.) [62].

3.2. Adult Donation. In 2006, Koffron et al. [63] described the first hand-assisted laparoscopic RH for live donation. Kurosaki et al. [64] reported in the same period 13 consecutive video-assisted adult-to-adult laparoscopic hepatectomies (3 RH and 10 left ± segment I hepatectomies): surgical manipulation was obtained via ports or via a 12 cm incision whilst view resulted by a combination of direct and laparoscopic vision. Reported median operation time was 363 ± 33 minutes and a median blood loss of 302 ± 191 mL. No complications were reported, restoration of liver function was smooth, and analgesics use was inferior with respect to the historical control (median: 1.2 versus 3.8 times).

In 2008, the transplant group from Seoul [65, 66] commented on the first series of hand-assisted laparoscopic modified RH preserving the middle hepatic vein; the authors reported 2 cases of laparoscopic RH and 7 cases of laparoscopy-assisted RH with a hand-port device. Hilar dissection and parenchymal transection were performed under pneumoperitoneum ($n = 2$) or through a minilaparotomy incision ($n = 7$). The graft was extracted through the site of the hand-port device or the minilaparotomy. Operative time was 765 and 898 min in the laparoscopic RH patients, and it ranged from 310 to 575 min for the laparoscopy-assisted surgery. In one case, a fluid collection along the liver resection margin was reported, but it was resolved after percutaneous drainage.

At the Northwestern University, Baker et al. [67] retrospectively compared 33 open versus 33 laparoscopic living donor RHs, suggesting that laparoscopy could present equivalent safety, resource utilization, and effectiveness, with several adjunctive physical and psychological benefits. Donor operative times were shorter for the laparoscopic group (265 min versus 316 min). Blood loss and length of stay were comparable. Additionally, total hospitalization costs were equivalent. Finally, the group from Seoul compared single-port laparoscopy-assisted donor right hepatectomy ($n = 40$) with laparoscopy-assisted donor right hepatectomy ($n = 20$) and open donor right hepatectomy ($n = 90$); postoperative complication and reoperation rates revealed no significant differences, the single-port group showing the lowest level of postoperative pain [68].

Although very limited experiences have been reported worldwide until now, no mortalities have been encountered in laparoscopic living donor hepatectomy, whether adult or paediatric. Larger experience is needed in this field, but only centres with a coincident expertise in hepatic mini-invasive surgery and living donor LT should approach this type of surgery.

4. Laparoscopic-Assisted Liver Transplantation

The first nine cases of living donor LT through a short-midline incision combined with hand-assisted laparoscopic surgery have been reported in Japan [69]. All the patients were cirrhotic (median MELD score 14). Total hepatectomy was carried out through a hand-assisted laparoscopic approach with an 8 cm upper midline incision. Explantation of the diseased liver was obtained through the upper midline incision which was extended to 12 to 15 cm. Partial liver grafts were implanted through the upper midline incision. Median surgical time was 741 min, and the median blood loss was 3,940 g.

This preliminary report of application of laparoscopy during LT procedure represents an extraordinary innovation, opening new porspectives in this fascinating surgical field. Further evolutions in the use of mini-invasive surgery in LT are expected in the next years.

5. Laparoscopic Posttransplant Surgery

Postoperative laparoscopic management of LT patients is less common with respect to renal transplant recipients: in fact, laparoscopy is easily applied after kidney transplantation, given the fact that in this type of transplant the dissection is completely extraperitoneal.

In postLT patients, laparoscopy is a useful tool to solve a number of surgical complications; however, its use is strictly connected to surgeon's experience and versatility.

5.1. Laparoscopic Incisional Hernia Repair. Incisional hernia is caused by several aetiologies, many of whose could be concomitantly observed in LT recipients: advanced age, wound infection, ascites, steroids, diabetes, surgical techniques, suture material, retransplantation, bilateral subcostal incision with midline extension, and, not less important, surgeon's experience. The most common site for incisional hernia in LT patients is located at the junction of the transverse and upper midline incisions [70]. In literature, the incidence of incisional hernia varies from 5% to 17% [71]. Large incisional and ventral hernias in nontransplant patients are now routinely repaired using laparoscopic technique. Laparoscopic ventral hernia repair seems to have a reduced risk of recurrence and infection compared to standard repair [72]. In LT patients, laparoscopic hernia

repair is safe and with similar results when compared with open repair [70, 73].

Andreoni et al. [74] successfully completed 12 out of 13 attempted incisional hernia repairs by the laparoscopic technique in LT patients. Gore-Tex mesh was used. At the time of publication, they report no recurrence. They concluded that laparoscopic mesh repair of incisional hernias is practical and safe in patients with a surgical history of LT transplantation, with a low incidence of infections and no recurrence. However, in a monocentre study [74], a higher rate of postoperative seroma was observed in LT with respect to nontransplanted patients [75]. A study from Germany analyzed a population of 29 solid organs recipients: 15 cases were treated with intraperitoneal onlay mesh repair and 14 with conventional hernia repair [76]. Recurrence rate was 6% versus 50%, and complication rate was 33% versus 21% in laparoscopy and conventional groups, respectively.

A study from Spain described 20 cases of laparoscopic incisional hernia repair in patients after LT, using a Bard Composix mesh, showing excellent results and few complications [77]. Observing the excellent results obtained using laparoscopy for the treatment of incisional hernia in LT patients, we can conclude that it could be safely performed also in this particular type of patients, and it could be considered a standard practice, mainly in an expert surgeon's hands.

5.2. Other Indications. In the last years, different uses of laparoscopy have been attempted in LT recipients. Merenda et al. [78] reported two cases of intestinal occlusion caused by adhesions and three cases of lymphocele, all approached with laparoscopic surgery. In all cases but one, the authors were able to complete the surgery by laparoscopic means; in one of the two occlusions, the procedure was switched to laparotomy because of a choledochojejunal anastomosis lesion.

Gill et al. [79] reported a single case of a right adrenalectomy after LT in a 63-year-old female patient with a right adrenal mass and a previous story of left radical nephrectomy for a renal cell carcinoma and LT for primary biliary cirrhosis. A laparoscopic right adrenalectomy via the retroperitoneoscopic approach was successfully performed, and the patient was discharged home on the first postoperative day.

DeRoover and Sudan [80] documented the case of a 46-year-old female transplanted for primary sclerosing cholangitis who presented multiple splenic aneurysms and abdominal pain: after a laparoscopic splenectomy, the patient was discharged on postoperative day 3 free of symptoms. A Japanese experience [81] reported 5 cases of hand-assisted laparoscopic splenectomy for hypersplenism in living donor LT recipients. On the basis of the excellent results, the authors consider it as a possible standard procedure after LT.

Robles et al. [82] commented on 2 cases of biliary peritonitis after T-tube removal who failed conservative treatment and subsequently underwent laparoscopy: lysis of adhesions was carried out in the right upper quadrant, a Penrose drain was placed, and both patients were discharged home on postoperative day 4. In 2010, Zhu et al. [83] reported the first total laparoscopic hysterectomy after LT. Authors confirmed that no viscera adhesions were observed to the undersurface of the umbilicus.

In 2011, Lee et al. [84] were the first to successfully complete a laparoscopic total gastrectomy in a previously transplanted 72-year-old patient, showing that laparoscopy is a feasible method for gastric cancer treatment in LT patients.

Finally, the Hannover group reflected on the applicability of laparoscopy in the management of posttransplantation lymphoproliferative disorder in a pediatric population: 6 out of 34 (18%) solid organs recipients underwent laparoscopic biopsies because of the lack of superficial lesions, with a 83% success rate. In one patient, a trocar metastasis was identified and treated successfully with chemotherapy [85].

Despite few cases have been reported until now, we can affirm that several "conceptual" barriers in the field of laparoscopy have been overcome: previous LT no longer represents an absolute contraindication for laparoscopy; not only in case of small procedures (biopsies) or submesocolic and pelvic surgery, but also when supramesocolic organs are involved. Further experience is needed in this field and only surgeons with a high expertise in mini-invasive procedures must approach this type of surgery. However, the authors are confident that in the future laparoscopic or robotic surgery will substitute open surgery in many cases even in previously transplanted patients.

6. Conclusion

Use of laparoscopy in the field of LT is safe and feasible. Mini-invasive approach is commonly adopted in the bridge treatment of HCC in patients waiting for LT: in case of LLS, laparoscopic procedure is recognized as the gold standard therapy. In living donor hepatectomy, and, recently, in LT, pure mini-invasive approaches or hybrid forms of laparoscopic and open surgery have been attempted. However, a limited number of reports are currently available on this subject, and great ability and confidence are recommended for starting these laparoscopy-assisted programs. Laparoscopy for abdominal surgery after LT has been demonstrated to be feasible and safe, not only in patients candidates for pelvic surgery, but also in case of surgery in the upper abdominal quadrants. In the next future, welcome improvement in technologies will give impulse to further expansion of this surgical area.

Conflict of Interests

There is no conflict of interests to declare.

Authors' Contribution

Q. Lai designed the study; Q. Lai, R. S. Pinheiro, G. B. L. Sandri and G. Spoltini wrote the paper; F. Melandro, N. Gugliemo, M. D. Laudo, F. M. Frattaroli, P. B. Berloco and M. Rossi participated in the critical evaluation of the paper.

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