



## Special article

# VI Consensus Document by the Spanish Liver Transplantation Society<sup>☆,☆☆</sup>



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## A B S T R A C T

The goal of the Spanish Liver Transplantation Society (*La Sociedad Española de Trasplante Hepático*) is to promote and create consensus documents about current topics in liver transplantation with a multidisciplinary approach. To this end, on October 20, 2016, the 6th Consensus Document Meeting was held, with the participation of experts from the 24 authorized Spanish liver transplantation programs. This Edition discusses the following subjects, whose summary is offered below: (1) limits of simultaneous liver–kidney transplantation; (2) limits of elective liver re-transplantation; and (3) liver transplantation after resection and hepatocellular carcinoma with factors for a poor prognosis. The consensus conclusions for each of these topics are provided below.

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## VI documento de consenso de la Sociedad Española de Trasplante Hepático (SETH)

## R E S U M E N

La Sociedad Española de Trasplante Hepático tiene como objetivo la promoción y elaboración de documentos de consenso sobre temas de actualidad en trasplante hepático de abordaje multidisciplinario. Para ello, el 20 de octubre de 2016 se celebró la VI Reunión de

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Trasplante hepatorenal  
Retrasplante hepático

consenso con participación de expertos de los 24 programas de trasplante hepático españoles autorizados. En esta edición se han abordado los siguientes temas, cuyo resumen ofrecemos a continuación: 1. Límites al trasplante simultáneo de hígado-riñón; 2. Límites del retrasplante hepático electivo; y 3. Trasplante hepático tras resección y hepatocarcinoma con factores pronósticos de gravedad. Se exponen a continuación las conclusiones consensuadas de cada uno de estos tópicos.

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## Limits of Simultaneous Liver–Kidney Transplantation

Simultaneous liver and kidney transplantation (LKT) aims to improve the survival of patients with end-stage liver and kidney disease. There is an acceptable consensus in the indication of simultaneous LKT in patients with decompensated cirrhosis and end-stage renal failure on chronic dialysis. However, both nationally and internationally, there is significant heterogeneity in the criteria for simultaneous LKT when it comes to non-cirrhotic or compensated liver diseases, or for liver transplantation candidates with kidney failure and moderate-severe reduction of the glomerular filtration rate.<sup>1</sup>

The primary objective of this consensus meeting organized by the SETH was to promote discussion and unify criteria for the indication of simultaneous LKT by the liver transplant groups in Spain. Despite the MELD prioritization used by most transplant programs, simultaneous LKT activity has not significantly increased in Spain in the last 6 years (30–35 LKT/year). However, given the shortage of donors and waiting-list mortality, it is still necessary to optimize the use of transplanted organs. The objectives of the meeting regarding simultaneous LKT focused on: (a) avoiding liver transplantation (LT) in candidates for kidney transplantation (KT) whose liver prognosis is good; (b) avoiding KT in candidates for isolated LT with recoverable acute renal failure; (c) defining criteria for rare diseases; and (d) achieving patient survival with appropriate and equitable treatment intention for all groups.

In order to present the main controversial situations, the following topics of discussion were posed:

1. Candidate for kidney transplant with cirrhosis of the liver and no criteria for liver transplant per se: criteria for simultaneous liver–kidney transplantation.
2. Candidate for liver transplant with end-stage chronic kidney disease: criteria for simultaneous liver–kidney transplantation.
3. Candidate for liver transplant with acute kidney injury (AKI): criteria for simultaneous liver–kidney transplantation and role of biopsy and non-invasive markers.
4. Criteria for simultaneous liver–kidney transplantation in hyperoxaluria and polycystic liver and kidney disease.
5. Specific donor criteria for simultaneous liver–kidney transplantation.

In each of these five blocks, several specific questions were posed and debated before a final vote on the conclusions. Conclusions were established as recommendations when 3/4 of the liver transplant groups were in agreement.

## Candidate for Renal Transplant With Cirrhosis of the Liver and No Criteria for Liver Transplant per se: Criteria for Simultaneous Liver–Kidney Transplantation

Studies about the natural history of chronic liver disease establish criteria for LT for decompensated cirrhosis, especially when there is a decline in liver function. In some patients with advanced chronic liver disease, with no criteria for LT but with criteria for KT, kidney transplantation could significantly accelerate the progression of the liver disease as a consequence of surgery, post-transplant complications and the use of immunosuppression. It was considered acceptable to propose simultaneous LKT for patients with chronic compensated liver disease with a high risk (more than 10%) for presenting criteria of isolated LT in the 3 years following a KT. In the group of patients with compensated cirrhosis, the parameter that best predicts the risk for decompensation of the liver disease is the hepatic venous pressure gradient (HVPG). Specifically, patients with compensated cirrhosis and no clinically significant portal hypertension (HVPG <10 mmHg) have a probability of decompensation within 4 years below 10%.<sup>2–4</sup>

- In the scenario of patients with end-stage chronic kidney disease who are candidates for RT and present compensated cirrhosis of the liver with good hepatocellular function (Child-Pugh's stage A), in which cases is simultaneous LKT indicated?

**Recommendation 1.** Simultaneous liver and kidney transplantation is indicated in patients with indication for renal transplant who present liver disease with significant portal hypertension (GVPH  $\geq 10$  mmHg) or presence of esophageal varices.

Evidence/recommendation IIB<sup>1</sup>

**Recommendation 2.** Candidates for simultaneous LKT do not require any additional criteria for prioritization on the waiting list beyond the MELD score.

Evidence/recommendation IIIB

It was discussed whether the esophageal varices were candidates for primary prophylaxis (medium-large, or small with signs of risk). It was specifically established that thrombocytopenia ( $<100\,000\text{ mm}^{-3}$ ) or hypoalbuminemia

<sup>1</sup> Levels of evidence according to the Center for Evidence-Based Medicine of Oxford.

(<2.8 g/dL) would not be considered criteria for significant portal hypertension per se. The use of non-invasive detection methods (elastography) should be assessed in these patients, although there currently is not sufficient information to be able to include them. Additionally, it was recommended in patients positive for the hepatitis C virus (HCV) to always attempt antiviral treatment before considering LKT, as well as treating the remaining factors that could favor the progression of the liver disease. As for candidates for KT with cirrhosis due to non-alcoholic steatohepatitis, no specific recommendation was established by the work group due to the absence of current evidence.

#### **Candidate for Liver Transplant With End-stage Chronic Kidney Disease: Criteria for Simultaneous Liver–Kidney Transplantation**

Chronic kidney disease (CKD) is defined as the presence of chronic kidney structure damage with a glomerular filtration rate (GFR) below 60 mL/min for more than 3 months. Several studies indicate a decrease in survival of isolated LT as the GFR decreases, and there is shorter survival of patients who have undergone isolated LT compared to simultaneous LKT in patients on chronic dialysis. Previous consensus documents about this recommendation were discussed,<sup>3,5,6</sup> and the data support these agreements. Formulas that estimate GFR based on creatinine notably overestimate (up to 30%–40%) the actual GFR in patients with cirrhosis and renal function decline.<sup>7</sup> Data from large series of isolated LT demonstrate that the presence of CKD with GFR less than 30 mL/min persistently maintained in the pretransplant phase is associated with a higher risk for terminal CKD and mortality one and 3 years post-transplant.<sup>8,9</sup> Finally, the caseload from 2005 to 2013 of the United Network for Organ Sharing (UNOS) indicates an 8%–10% risk of need for dialysis or kidney transplantation in the first year after isolated LT for recipients with CKD and GFR below 30 mL/min.<sup>10</sup> Finally, predictors for declining renal function, such as proteinuria, diabetes and renal histological data, were evaluated.<sup>8</sup>

- In the scenario of patients with liver transplant criteria who also present CKD (defined as a GFR less than 60 mL/min for more than 3 months), in what cases is simultaneous liver–kidney transplantation considered indicated?

**Recommendation 3.** *Simultaneous liver and renal transplantation is recommended in patients with liver transplant criteria plus:*

*CKD with chronic dialysis or estimated GFR less than 30 mL/min. CKD with estimated GFR between 30 and 40 mL/min with some sign of poor renal prognosis, such as proteinuria >1 g/24 H (>3 months) and/or diabetic nephropathy; and/or histological findings of poor prognosis in renal biopsy (more than 30% glomerulosclerosis or more than 30% interstitial fibrosis).*

*Evidence/recommendation IIIB*

GFR could be calculated with formulas (MDRD6 or MDRD4), although measurement is recommended using a radioisotope

(iothalamate). Renal biopsy is recommended, depending on the risks and benefits in patients with poor coagulation.<sup>10</sup>

#### **Candidate for Liver Transplant With Acute Renal Injury: Criteria for Simultaneous Liver–Kidney Transplant and Role of Non-Invasive Markers and Biopsy**

Previous consensus documents<sup>3,5,6</sup> were reviewed, as well as the surgical criteria currently used by UNOS.<sup>10</sup> The new AKI (acute kidney injury) definitions were adopted according to the definition of the International Club of Ascitis,<sup>11,12</sup> as well as the definition of its grades to make decisions about this type of patients. We analyzed the predictive factors for AKI reversibility and their limitations, the difficulty and poor performance of renal biopsy in these patients, and the absence of reliable biomarkers.<sup>13</sup> However, the absence of renal function recovery in patients with AKI usually correlates with time on dialysis, the persistence GFR below 30 mL/min<sup>14</sup> and the cause of AKI.<sup>15</sup> The main prognostic indices described for this type of patients were presented,<sup>16–18</sup> although they have not been validated in our setting.

- In the scenario of patients with LT criteria who also present sustained acute kidney disease (GFR lower than 60 mL/min for less than 3 months), in which cases is simultaneous LKT considered appropriate?

**Recommendation 4.** *Simultaneous LKT is recommended in patients who are candidates for LT with acute kidney disease who require dialysis for 6 consecutive weeks, either continuously or intermittently.*

*Evidence/recommendation IIIB*

It is necessary to evaluate the cause of renal dysfunction in order to establish its potential reversibility and the individualization of renal biopsy according to risk-benefit. The GFR was not considered per se a criterion for indication of simultaneous LKT in this context. Neither was special prioritization on the waiting list considered necessary for these patients. For those who end up receiving an isolated LT and do not recover renal function after transplantation (maintaining a GFR less than 30 mL/min), RT waiting list prioritization is recommended.

#### **Criteria for Simultaneous Liver–Kidney Transplantation in Other Indications**

##### **Primary Hyperoxaluria Type 1**

Primary hyperoxaluria type 1 is an autosomal recessive metabolic disease caused by deficiency of the enzyme alanine-glyoxylate aminotransferase, which is synthesized in the liver. A genetic study is essential for confirmation because only type 1 is cured with LT. It is one of the main indications for simultaneous LKT, especially in children and young adults. Isolated KT has very poor results due to the persistence of the disease, with much lower graft and patient survival rates compared to simultaneous LKT. Consensus

documents and bibliographic data were reviewed, which restrict isolated LT to individual cases with a GFR higher than 40 mL/min, although this situation is exceptional in young adults.<sup>19,20</sup>

- In the scenario of patients with primary hyperoxaluria type 1, in which cases are simultaneous LKT considered indicated?

**Recommendation 5.** Simultaneous LKT is indicated in patients with primary hyperoxaluria type 1 with GFR less than or equal to 40 mL/min, considering only isolated LT for pediatric cases with GFR greater than 40 mL/min.

*Evidence/recommendation IIIIB*

This group of patients with primary hyperoxaluria type 1 does not require any specific prioritization criteria beyond the MELD, although this can be individualized according to the presence of oxalosis. Furthermore, the use of liver grafts from patients with primary hyperoxaluria type 1 for domino LT is contraindicated as it precipitates early onset of the disease.

#### Polycystic Liver and Kidney Disease

Polycystic liver disease can occur in 2 genetically different situations: autosomal dominant polycystic kidney disease (ADPKD), which is associated with polycystic liver disease in 70%–80% of cases, and polycystic liver disease (PCLD).<sup>21</sup> Recent data in our setting indicate that it is a growing problem. The series of polycystic liver and kidney disease transplants were reviewed, which showed that 42% received simultaneous LKT and 58% isolated LT. In the latter group, 14% later required RT. The results of LKT due to polycystic disease were similar to other indications of LKT.<sup>22</sup>

The indication for liver transplantation in patients with polycystic liver and kidney disease is determined by symptomatic and disabling diffuse liver involvement, including space occupying symptoms (satiety, gastrointestinal disorders, dyspnea, etc.), compression of structures (Budd-Chiari syndrome, biliary compression), portal hypertension (presence of esophageal varices, hemorrhage due to varices, and/or ascites), untreatable complications of hepatic cysts (infection, hemorrhage) and malnutrition.<sup>21</sup> On the other hand, the indication requires that there be no alternative treatment for the specific case.

- In patients with polycystic liver and kidney disease, in which cases are simultaneous LKT considered indicated?

**Recommendation 6.** Simultaneous LKT is indicated in patients with polycystic liver and kidney disease with indication for LT and renal involvement with a GFR below 40 mL/min.

*Evidence/recommendation IIIIB*

In all cases, it is recommended to assess individualized criteria for progression of the renal disease (for example, a

drop in GFR), as well as any increase in the size of the cysts and population risk factors.<sup>23</sup>

#### Specific Donor Criteria for Simultaneous Liver–Kidney Transplant

As a final block of discussion, specific donor criteria were discussed, given the increased age range of the donors. Classically, donors without extended criteria were considered suitable donors for simultaneous LKT and those under the age of 60 were considered apt, while donors between the age of 50 and 59 years were required to have no history of arterial hypertension or diabetes. This strict criterion limits access to transplantation to patients who are candidates for LKT, on the one hand, while selecting the best donors for this group of patients. These considerations led to the debate of extending the criteria to accept donors for simultaneous LKT recipients, in a similar way to isolated KT recipients.<sup>24</sup>

The SETH considers the possibility of accepting donors between 60 and 70 years of age with no other risk factors for LKT, provided that the recipient is over 60 years of age. In this case, a renal biopsy will also be considered.

Regarding the possible acceptance of donors in asystole for LKT, there are currently not enough reports in the literature to support this option, and there are no data on the results of donors in asystole with normothermic recirculation.<sup>25,26</sup> Therefore, acceptance of donors in this circumstance is open for future evaluation.

**Recommendation 7.** It is recommended to use donors younger than 70 with no history of arterial hypertension and/or diabetes, or donors <60 when arterial hypertension and/or diabetes are present. In cases of doubt, the use of renal biopsy is mandatory.

*Evidence/recommendation III*

#### Limits of Elective Liver Re-transplantation

According to the Spanish Liver Transplant Registry, more than 20 000 LT have been performed in Spain in the last 3 decades surpasses, with one-, 5-, 10- and 15-year patient survival rates of 85.1%, 72.6%, 62% and 52.4%, respectively.<sup>27</sup> These results vary depending on the etiology, stage, recipient and donor characteristics, as well as having received a previous liver graft and at what moment.

Despite the fact that medical and surgical advances have emerged over the years, some patients who have received LT will develop early or late-onset complications that will result in the failure of the transplanted organ, and liver retransplantation (ReLT) will be the only definitive therapeutic option. National and international registries report ReLT rates that range between 7% and 13%.<sup>27–29</sup>

In recent years, this has led to renewed interest in ReLT among scientific societies and LT groups. ReLT is the only therapeutic alternative for patients with irreversible graft dysfunction. Given the shortage of organs, there may be an ethical conflict between assigning an organ to a patient who has not had a previous opportunity vs one who needs a retransplant.



ReLT can be indicated at any time after the first LT but, in general, 2 types of ReLT are distinguished according to when they are indicated or performed: (1) the so-called early, acute or urgent ReLT (ReLTu), when graft failure occurs in the first days after the first LT and is due to primary dysfunction, initial insufficient function, hepatic artery thrombosis, uncontrolled acute rejection or other technical issues; and (2) elective (ReLTe) or delayed liver retransplantation, which usually occurs months or years after the first LT and usually occurs due to recurrent disease, technical problems (usually biliary in origin) or chronic rejection.<sup>30</sup> Although there is no generalized agreement in the literature on a specific time point to define urgent and elective ReLT, for the purpose of this document we have followed the criteria established by the ONT (Spanish National Transplant Organization) regarding the allocation of grafts in an emergency, and we have defined ReLTu as retransplantation performed during the first week post-op, while retransplantations indicated and occurring at least 8 days after the first LT were considered ReLTe.

### **Incidence of Elective Liver Retransplantation in Spain**

The need to perform ReLT in Spain is approximately 6%.<sup>31</sup> According to data published in different series by groups or national registries, the incidence varies from 5 to 22%.<sup>27,32,33</sup> The national consensus of the Spanish LT groups establishes that the desirable standard ReLT rate should be less than 10%, which could be deemed an indicator of quality care in the immediate post-transplant period and of activity in the long-term post-transplant period.<sup>34</sup>

After the analysis of the responses to the survey of 25 Spanish hospitals about the transplantation activity over the past 5 years, with 4674 LT performed in the adult population and 178 in the pediatric population, it can be observed that the ReLTe rate is 4.8% and therefore within the limits established by the scientific society.

The differences observed between the different transplant centers according to the Spanish Liver Transplant Registry may be explained by the lack of homogeneity in the criteria for inclusion on the waiting list for ReLT. Although the criteria for an urgent ReLT are well established by the ONT and accepted by the transplant groups, the same is not true for ReLTe, hence the need to evaluate this indication.

In recent years, the effect of hospitals' surgical volumes has been highlighted as a measure of quality and safety in diagnostic and therapeutic procedures, aimed at evaluating the results of certain procedures<sup>35</sup> in correlation with the experience of a multidisciplinary group, the greater ability to recognize and treat complications, etc. There are studies that do not support this hypothesis,<sup>36</sup> as in the case of ReLTe, because the increased risk of these patients is usually due to the fact that they are more deteriorated individuals and the greater technical difficulties of the procedure. Although there are data suggesting that performing these procedures at larger medical centers achieves higher one-year patient survival rates, the same is not true for one-year graft survival, which suggests that the ReLT volume could be an imprecise measure of the results.

Spanish transplant units perform an average volume of liver transplants of 15–100 year<sup>-1</sup>, including centers with high LT volumes >70 LT/year, mean (35–69 LT/year) and low

<34 LT/year. Not all centers perform the same number of transplants, nor do they all have the same years of experience with the liver transplant program, nor are the criteria for access to ReLTe identical.<sup>37</sup>

The high volume of the transplant center could have a negative impact on survival if borderline indications are accepted, taking into account that, in the MELD era, patients who access primary LT or ReLTe do so in more deteriorated situations. In addition, some authors report that transplant units with greater volumes and experience accept grafts with a higher donor risk index.<sup>38</sup>

### **Indications for Elective Liver Retransplantation in Spain**

The analysis of the indications for ReLT in the different series<sup>39</sup> reveals that hepatic artery thrombosis is the most common indication for ReLTe (31.6%), followed by chronic rejection (22.4%) and the recurrence of the baseline disease (13.2%). Other indications such as primary graft dysfunction and acute rejection are responsible in a lesser proportion.

Over the years, it has become necessary to strictly select indications for ReLT. Years ago, the indications for ReLTe were more liberal, but nowadays multidisciplinary committees tend to limit these indications based on the identification of recipient risk factors at the time of the indication and liver retransplantation.

Underlying diseases have been evaluated as prognostic factors for ReLTe results, although no significant differences have been found among the different indications for ReLTe (recurrence of primary disease, chronic rejection, biliary complications, etc.). Although it is true that the incidence of liver disease due to HCV has increased in our country during the period of analysis, this will presumably not be the case in the coming years given the efficacy of the new antiviral agents available.

The need for liver grafts is higher than that of available grafts,<sup>40</sup> which is why it has been proposed that ReLTe should be limited to patients with a good prognosis in order to maximize the use of scarce resources<sup>41,42</sup> and to achieve 5-year graft survival results over 50%,<sup>39</sup> a fact that seems to confirm the viability and usefulness of ReLTe under the selection of those ideal conditions. Recent single-center studies support these results, establishing improvements in survival results in all patient groups in recent years.<sup>43</sup>

In the descriptive analysis of the surveys conducted in Spanish groups, biliary problems of ischemic origin (ischemic cholangiopathy) were the most frequent cause of ReLTe (23.7%) from 2011 to 2015, followed by recurrence of HCV (21%), chronic rejection (14.6%) and late-onset or chronic liver graft dysfunction (6.8%).

### **Age Limit for Liver Retransplantation**

In Spain, the age of ReLTe recipients is slightly lower than that of primary LT recipients (47.9 years vs 52.9 years) in the study by Torres-Quevedo et al.<sup>44</sup> However, Saborido et al. and Bernal et al.<sup>45,46</sup> did not find significant differences in their respective studies. In the analysis of the OPTN registry including more than 35 000 patients, Kim et al.<sup>41</sup> also observed a lower age in the recipients of a ReLT than in the recipients of a first LT (48.9 and 52.4 years, respectively). We could suggest that the

experience of the groups in the recent period analyzed, the improvement in the surgical technique and the better patient selection is contributing to this slight escalation in the age of ReLT recipients.

The ages most represented among ReLT recipients of the Spanish Retransplant study<sup>47</sup> are concentrated between 40 and 59 years of age (61.6%), with a lower proportion in the group  $\geq 60$  years, possibly influenced by the difficulties involved in indicating ReLT in patients at more advanced ages (comorbidities, life expectancy, biological age, etc.); in contrast, there is a greater proportion of retransplanted patients at younger ages (18–39 years), justified by the greater expected life gain and fewer comorbidities in younger patients.

More than two-thirds of the hospitals surveyed (63.3%) consider that there should not be an age limit different than what is used to indicate an initial LT. Those who believe that there should be an age limit for access to ReLT believe that it should be between 65 and 70 years of age, after considering the associated comorbidities.

**Recommendation 8.** Possible ReLT recipients should not be excluded for their age.

*Evidence/recommendations IIIC*

**Recommendation 9.** In recipients requiring ReLT, it is necessary to thoroughly evaluate comorbidities, especially in the older patient group.

*Evidence/recommendation IIIC*

### Survival of Elective Liver Retransplantation

Most of the series analyzing the survival of ReLT belong to multiple-center studies, and include both types of ReLT (urgent and elective). The first survival results of ReLT were found in a multicenter study published in 1985 among the first patients who underwent ReLT,<sup>48</sup> where not only inferior results were observed, but also an increase in survival in the most recent stages, as expressed in national and international studies<sup>47,49</sup> reporting one-, 3- and 5-year survival rates of 67%, 58.4% and 53.1%.

The SETH consensus document published in 2008<sup>50</sup> recommends offering ReLT after the failure of the first liver graft when the indications guarantee a 5-year patient survival rate  $>50\%$ . 91% of the hospitals surveyed consider that ReLT indications should follow the standard proposed by the SETH in terms of survival like any other indication for LT.

**Recommendation 10.** The 5-year survival rate of ReLT should exceed 50%.

*Evidence/recommendation IIIB*

### Comorbidities in Elective Liver Retransplant

The overall survival analysis of elective liver retransplantation shows how the greatest decrease in survival occurs during the first year post-transplant, hence the importance of identifying prognostic factors related to the recipient that may be

modifiable before the procedure. If their modification is not possible, liver retransplantation should be contraindicated, either before getting on the waiting list or during hospitalization. This observation has been confirmed in studies, such as Crivellini et al.,<sup>51</sup> where the highest mortality occurred in the first 2 months after ReLT and the independent predictors for 90-day mortality were: renal function (preoperative creatinine  $>2$  mg/dL), recipient  $>50$  years, as well as the intraoperative use of blood products.

Among the main situations that Spanish transplant units considered contraindications to initial ReLT were the presence of non-revascularizable vascular thrombosis (95%), advanced renal failure (86%), severe malnutrition (86.4%) and, although in a lower percentage, BMI  $>35$  (63.8%).

The SETH proposes that the evaluation of the possible candidate for ReLT should be similar to that carried out in candidates for a first LT, specifically examining aspects related with venous and arterial vascular permeability, renal function, cardiac function and nutritional status. The results of ReLT have improved in recent years, the highest mortality being concentrated during the first 3 months, a situation that is justified by factors related with the situation prior to liver retransplantation and the deterioration during the wait until the ReLT.

**Recommendation 11.** Vascular problems, renal dysfunction and nutritional state should be carefully evaluated before indicating ReLT as they could be considered a contraindication.

*Evidence/recommendation IIIC*

### Limits to the Number of Elective Liver Retransplantations

The need to perform urgent ReLT is decreasing progressively due to improvements in immunosuppressive therapy, surgical techniques, organ preservation and a better understanding of primary dysfunction.<sup>52</sup> On the other hand, the need for ReLT is expected to rise due to the increase in the number of LT carried out per year, which may lead to recurrence of the primary disease or the failure of the graft in the medium and long-term for different reasons.

The decision to offer a patient who has received a first LT a second chance is becoming an increasingly important issue, since ReLT has important implications, economically, ethically and in terms of results.<sup>53,54</sup> The situation becomes even more complicated in certain patient groups, such as senior transplant patients or in cases of viral diseases.<sup>55</sup>

50% of Spanish transplant teams believe that the number of grafts destined to perform ReLT in the same patient should be limited, with 2 grafts being the maximum that a recipient should receive, with special consideration of situations in pediatric patients and etiologies related with the technique.

**Recommendation 12.** The number of liver grafts that a recipient can receive should not be limited. However, the SETH recommends that after a first failed LT, the maximum number of grafts allocated to an ReLT recipient should be no more than 2. Special consideration could be given to the pediatric population and indications related with technical problems from the previous LT.

Evidence/recommendation IIID

### Predictive Models in Elective Liver Retransplant

Several models have been proposed to try to identify which patients are more likely to benefit from ReLTe and avoid this therapeutic alternative in the group of patients in whom survival is unacceptably low, although to date there is no universally accepted prognostic model.

Prognostic models attempt to predict the survival of ReLTe with preoperative variables, such as donor and recipient age, renal function, bilirubin levels, hot and cold ischemia time, C virus status, UNOS status, the need for mechanical ventilation and the time to the ReLTe. But these models should be improved by providing variables that consider changes in the patient's state during the wait and operative variables that in theory do not seem foreseeable. There are other models that include donor characteristics that may seem more complete and could improve the estimated probability of survival for a specific recipient at the time of ReLT; however, these models are complex and not widely accepted today.<sup>55</sup>

The Rosen model calculates risk scores based on the age of the recipient, bilirubin, creatinine and the interval from LT to ReLTe, establishing cut-off values that classify patients into different risk groups after retransplantation.

The MELD model, based on bilirubin, creatinine and INR, predicts the 3-month survival of patients with terminal-phase cirrhosis. Most organ allocation systems for LH and ReLTe use this score, considering it the best predictor of waiting list mortality. Nonetheless, although ReLTu in our country is guaranteed the highest preference (urgency 0) the first days after primary LT, ReLTe is classified by the MELD system for the allocation of an organ and competes with the other indications for LT on the waiting list.

The MELD model is the basis on which the organs in the ReLTe are allocated in most Spanish groups (86.4%), assigning the organs to the patients who need them most.<sup>56</sup>

**Recommendation 13.** *It is necessary to use a score to indicate ReLTe, the most frequently used being the MELD score.*

Evidence/recommendation IIIC

### Score for Contraindicating Elective Liver Retransplant

Some studies have suggested that the MELD model also predicts mortality after ReLTe,<sup>57</sup> with worse results in patients transplanted with higher MELD. Hence, the MELD score is an accurate indicator of mortality of patients waiting for ReLTe.<sup>55,58</sup> Generally, patients who undergo ReLTe have higher MELD scores due to higher levels of bilirubin and serum creatinine, which, together with the technical and infectious problems of ReLTe, cause survival to be reduced.

Several groups have confirmed the direct correlation between the increase in MELD scores at the time of ReLTe and the mortality of the procedure,<sup>59,60</sup> so that survival is reduced to less than 60% during the first year for recipients with MELD >25.<sup>55</sup> In order to improve the results of the ReLTe,

it should be attempted with a MELD score lower than that used for the first LT. This principle is illustrated in the study by Burton et al.,<sup>53</sup> where the maximum value for retransplantation was achieved with a MELD score of 21 for HCV-positive patients and 24 points for HCV-negative patients.

With the data of 1356 adults undergoing UNOS ReLT, Rosen et al.<sup>61</sup> validated a model of easy applicability that serves as a complement to clinical decision-making when establishing the contraindication to ReLT. The study confirmed that the preoperative status of a liver retransplant recipient based on age, bilirubin and serum creatinine is of utmost importance, together with the time elapsed since the first LT for the prediction of survival after ReLTe, and establishes the possibility of predicting survival at 2-3 years, based on 3 risk groups (low, moderate and high), with a direct impact on morbidity, mortality and direct procedure costs.<sup>62,63</sup>

In the analysis by risk categories, the Spanish groups agree with Rosen et al. in that the patient groups with low and moderate risk are those with better survival. However, the survival of ReLTe with a high Rosen index is greatly diminished and does not seem acceptable according to the recommendations of the SETH consensus document,<sup>50</sup> because they only reach survival rates of 43.9% in the first year, 35.5% within 3 years and 26.3% in the 10 years after the retransplant according to the Retrasplan study.<sup>57</sup> The variables that predict these results have a greater impact in the immediate post-transplant period, contributing to the most marked decrease in survival during the first year in the 3 risk categories, although it is more pronounced in the high risk group. These results are similar to those established by Linhares et al.<sup>64</sup>

93% of Spanish hospitals have adopted the Rosen model as a system for assessing candidates for ReLTe when deciding whether there is a contraindication for access to the waiting list. Thus, retransplantation is contraindicated for patients with Rosen index >20.5 (high risk) due to the low expected survival, whereas when the candidate has a <20.5 (low or moderate risk index), the expected one-year survival is 82% and 75%, respectively.

**Recommendation 14.** *The higher MELD score of patients at the time of the ReLTe entails greater deterioration and worse survival results, especially in patients with MELD >25.*

Evidence/recommendation IIIB

**Recommendation 15.** *The Rosen index is a good tool for classifying the severity of a recipient of a ReLTe and, together with clinical assessment, helps contraindicate or reconsider the best time for ReLTe.*

Evidence/recommendation II-2B

### Management of Candidates for Elective Liver Transplantation on the Waiting List

#### Prioritization on the Waiting List of Elective Liver Retransplantation

In Spain, candidates for ReLTe compete in the same organ allocation system as recipients of a first LT. Unlike what happens in other indications considered exceptions to MELD,

which receive some type of prioritization, such as hepatocellular carcinoma, refractory ascites, CBP, urgent ReLT, etc., ReLT has to wait for the MELD score to increase to be assigned a graft.

Spanish groups do not establish or apply any system of prioritization for patients waiting for ReLT, and 81.8% do not take into account the age of the recipient to establish any type of priority in organ allocation. In most patients, ReLT is indicated early and they are retransplanted with MELD <25, but the increase in MELD while on the waiting list (WL) leads to higher WL mortality and is expected to negatively influence survival results after ReLT. That is why there are groups that would support the need to prioritize this small group of patients in a way that prevents WL deterioration.

**Recommendation 16.** *No prioritization model surpasses MELD for establishing organ allocation.*

*Evidence/recommendation II-3B*

### Donors Assigned to an Elective Liver Retransplant

Donor characteristics have a significant impact on the results of ReLT, hence there are donor risk indicators for both a first LT and for ReLT. There are authors who value the quality of the graft in their predictive models, concluding that the quality of the new graft plays an important role in ReLT results.<sup>65</sup>

Usually, the groups do not have a specific ReLT matching policy between the quality of the graft and the state of the recipient, but one of the concerns is whether higher-risk donors should be considered for ReLT, given the poor results of this association. Although some studies have addressed this issue, none has shown any specific feature that contraindicates their use in ReLT.<sup>66,67</sup> The use of hepatic donors with expanded criteria for ReLT is a controversial issue. It is feared that these grafts, together with other donor characteristics, may have a direct influence on ReLT results. In some studies, advanced donor age was an independent factor associated with worse results, which is why it is recommended to avoid these donors in ReLT.<sup>68</sup>

Although there are authors who support the use of older grafts of advanced ages for ReLT, 68% of the Spanish groups consider we should avoid assigning grafts from senior donors (>70 years) and those with steatosis >30% to ReLT recipients because these factors are associated with increased graft loss rates, probably justified by ischemic changes and changes in liver synthesis function, which, together with occasionally longer ischemia times (>8 h) occurred during maintenance, surgery and preservation, could lead to poor early graft function. Despite this, one-third of the groups support the use of grafts from advanced age donors, supported by acceptable results in the literature.<sup>69,70</sup> considering that age alone should not be a barrier to directed donation to a first LT and future transplants, claiming that they provide survival rates similar to that of patients retransplanted with grafts from non-expanded donors.

The use of “unconventional” donors (livers from asystole, domino or living donors) has represented an increasing percentage of the donor pool offered in Spain. Although there

are not many reports from ReLT experiences in our country in the period 2011–2015, a priori two-thirds of Spanish groups will consider these grafts suitable to be implanted in ReLT recipients. However, partial split liver grafts are not considered adequate for ReLT recipients.

**Recommendation 17.** *Liver grafts from donors over the age of 70 and those with steatosis >30% should not be routinely accepted for ReLT.*

*Evidence/recommendation IIIC*

**Recommendation 18.** *Grafts from non-conventional donors (asystole, split, domino) could be considered adequate for ReLT.*

*Evidence/recommendation IIIC*

## Technical Aspects of Elective Liver Retransplant

ReLT is considered high-risk surgery by most surgeons and should therefore be performed by experienced surgeons and reference centers. Several challenges contribute to this degree of difficulty. First of all, due to the ever-present shortage of organs, patients must reach an advanced stage of the disease to be assigned a graft according to the organ allocation system (MELD), which, together with concurrent medical comorbidities, such as renal dysfunction, coagulopathy, recurrent infection and the chronic use of immunosuppression, increase the medical and technical complexity of these patients and the procedure, respectively. Secondly, the time elapsed after the first LT means that the anatomy is often distorted and surgical dissection is made difficult by the presence of dense vascular adhesions, which are present on many occasions together with portal hypertension and/or the presence of late-onset thrombosis of the hepatic artery, further complicating the ReLT surgical procedure.

The surgical technique proposed when performing ReLT does not differ from that of a first LT in Spanish groups, although portal hypertension can be aggravated during the retransplantation procedure, causing intestinal edema, increased intestinal permeability and bacterial translocation, which, together with the release of various toxic mediators, cytokines and endotoxins into the portal circulation,<sup>71,72</sup> can deteriorate the hemodynamic state of the recipients. In order to improve hemodynamic aspects of the recipient during surgery, retrohepatic vena cava preservation techniques (piggy-back) and portacaval shunts are proposed to avoid blood stasis in the region of the inferior vena cava and splanchnic artery, which are associated with less graft damage due to reperfusion ischemia, less intraoperative hemorrhagic phenomena and better graft survival, especially in grafts that are considered marginal.<sup>73</sup>

In general, Spanish groups perform the ReLT procedure with vena cava preservation techniques, but the technical difficulties for carrying out portosystemic shunting techniques can sometimes be the reason why it is performed in a lesser proportion than in a first LT. This beneficial effect is



more pronounced in recipients with high MELD score and in recipients of organs from marginal donors, so we should recommend using these shunting techniques whenever possible.

Arterial and venous complications are more frequent in the population of ReLTe patients than in the population of patients receiving their first LT, justified by the deterioration of vascular structures that often makes it difficult to perform the standard anastomoses. Therein lies the need for complete vascular studies prior to ReLTe to be able to foresee the use of vascular grafts or unusual locations of future venous or arterial anastomoses.

The biliary reconstruction technique in ReLTe seems to have a direct effect on survival results, which could indicate that the complications derived from these anastomoses are markers of graft dysfunction and a source of potential or recurrent infection, particularly when they are related to cholangitis.<sup>35</sup> The reconstruction techniques used are similar in a first LT and in ReLTe, although, according to the analysis data, the reconstruction most used in the ReLTe was choledocho-choledochal anastomosis (65.3%) with or without a T tube. We see a greater use of bilioenteric bypass techniques with defunctionalized Roux-en-Y loop in ReLTe than in the primary LT, which is a consequence of the high proportion of patients that develop problems associated with ischemia, cholangitis, stenosis, etc., and require manipulations of the biliary tract prior to ReLTe.

**Recommendation 19.** *The type of venous, arterial and biliary reconstruction in ReLTe does not differ from a first LT, unless the anatomical disposition creates a difficulty.*

*Evidence/recommendation III C*

### Liver Retransplant in Recurrent Hepatitis C Virus

Cirrhosis of the liver due to the hepatitis C virus (HCV) is one of the main indications for LT in most western countries. Hepatitis C recurs in the new graft in all viremic patients at the time of LT. Although the natural history of recurrent hepatitis C is relatively benign, approximately 20% of recipients develop graft cirrhosis within the first 5 years, and up to 10% have early aggressive recurrence in the form of severe cholestatic hepatitis.<sup>74</sup>

ReLTe is the only therapeutic option in patients with decompensated graft cirrhosis due to recurrent hepatitis C, but its use has been controversial because several studies showed worse survival years ago in this group of recipients compared to HCV-negative patients,<sup>75,76</sup> explained by the fact that viral recurrence had a negative impact on survival.<sup>53,77</sup> In addition, the antiviral treatments available until recently, which are based on interferon, had limited efficacy and were not free from side effects.

In recent years, the appearance of the new interferon-free regimens based on the combination of several direct-acting antiviral agents has dramatically changed the prognosis of patients with recurring hepatitis C with cure rates (sustained viral response) of 95%, few side effects and few interactions with immunosuppressive therapy.<sup>78-82</sup>

With current antiviral regimens, it is possible to successfully treat patients with cirrhosis of the decompensated graft before ReLT, with the hope that the eradication of the infection will improve the liver function and/or the clinical situation, to the point that the patients can be withdrawn from the ReLT waiting list. In very deteriorated patients, antiviral treatment can be postponed until after ReLT.

Therefore, the impression of Spanish groups is that there is no compelling reason to discriminate patients with severe recurrent hepatitis C from ReLTe, establishing the same criteria for evaluation, contraindication and allocation of organs as for other indications.

**Recommendation 20.** *There is currently no reason to impede the access to ReLTe of patients with severe hepatitis C recurrence post-LT.*

*Evidence/recommendation III C*

### Liver Transplantation After Resection and Hepatocellular Carcinoma With Factors for Severe Prognosis

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm and one of the most frequent causes of death in patients with cirrhosis of the liver.<sup>83</sup> The implementation of screening programs in the population at risk aims to detect tumors in initial stages, which are susceptible to receiving potentially curative treatments. In our setting, more than 80% of patients with HCC present underlying cirrhosis of the liver. Considering the only possibility to apply treatments with curative intent is by diagnosing the disease in an asymptomatic phase, and that this option is only feasible during the screening of the population at risk, biannual abdominal ultrasound screening is recommended to examine patients with liver cirrhosis in case they develop HCC.<sup>83</sup>

#### Criteria to Indicate Hepatic Resection

Currently, and based on the recommendations of the guidelines for the management of HCC,<sup>83-85</sup> surgical resection is considered the first option for the treatment of HCC in patients with compensated cirrhosis with normal bilirubin levels and without clinically relevant portal hypertension (CRPH).

The most accurate way to evaluate the absence of CRPH is by direct measurement of the pressure gradient at the suprahepatic vein; patients with a gradient below 10 mmHg are considered optimal for surgical resection.<sup>86</sup> The presence of esophageal varices or ascites confirms the existence of CRPH. However, the detection of splenomegaly and platelet count below 100 000 mm<sup>-3</sup> does not accurately identify the presence of CRPH.<sup>87</sup>

In recent years, the determination of hepatic stiffness by elastography has been evaluated as a tool to identify CRPH and thereby predict survival and liver dysfunction after surgical resection.<sup>88,89</sup> In this sense, a recent study by Llop et al.<sup>88</sup> demonstrated that elastography values higher than 21 kPa are highly suggestive of the presence of CRPH, and values lower

than 13.6 kPa are able to rule it out. Unfortunately, there is no clear cut-off value and, for the time being, elastography only allows the presence or absence of CRPH to be correctly classified in half of cases.

With these indications, HCC resection performed by experienced teams is associated with perioperative mortality rates of less than 10%, transfusion rates of less than 1% and 5-year survival of 70%–75%.<sup>83</sup> These recommendations are based on studies<sup>86,90,91</sup> demonstrating that the presence of CRPH is an independent predictor of high risk for clinical decompensation and mortality after surgical resection of HCC in patients with compensated cirrhosis of the liver. In the recent literature, there is a wide debate about the usefulness of the determination of CRPH as a prognostic factor, so that some authors argue that surgical resection should be offered as the first option for HCC treatment, regardless of the degree of PHT.<sup>91,92</sup> With the aim to determine the prognostic role of CRPH after surgical resection of HCC in patients with compensated liver cirrhosis, Berzigotti et al.<sup>93</sup> performed a meta-analysis confirming that the presence of CRPH correlates significantly with higher 3- and 5-year mortality rates and with a higher risk of clinical decompensation after surgery.

**Recommendation 21.** *Resection is considered the first treatment option for HCC in patients with compensated cirrhosis without clinically significant PHT.*

*Evidence/recommendation II-2B*

### Tumor Recurrence and Risk Factors

In spite of correct selection of candidates for surgery, surgical resection of HCC in patients with cirrhosis of the liver is associated with very high rates of tumor recurrence, which can reach 70% after 5 years.<sup>83</sup> It has been proposed that 60%–70% of recurrences are intrahepatic metastases that are not detected at the time of resection. They are usually single foci that appear during the first 2 years of follow-up, while 30%–40% of recurrences are considered de novo HCC, with a greater frequency of multiple foci and appearing at least 2 years post-op.

In most studies, the validated risk factors for tumor recurrence are tumor size, multinodularity or satellitosis, the presence of macro- or microscopic vascular invasion, and the low degree of cellular differentiation.<sup>87,94,95</sup> Given the absence of simple and effective diagnostic indicators for the early detection of postoperative HCC recurrence, multiple biochemical markers and/or gene expression analyses have been evaluated, which may help predict tumor recurrence. In this context, Fei et al.,<sup>96</sup> with the intention of evaluating the risk of recurrence based on variables related to inflammatory activity, show that the determination of the neutrophil/lymphocyte ratio (NLR) and the aminotransferase-to-platelet ratio index (APRI) before surgery are independent predictors of disease-free survival and overall survival in patients undergoing surgical resection for HCC. Likewise, an attempt has been made to evaluate the histological expression of certain genes as predictors for tumor recurrence. Zheng et al.<sup>97</sup> show that the low expression of the caudal type homeobox type 1

gene (CDX1) is significantly associated with poor prognosis and suggest that it could represent a new predictive factor for the prognosis of patients with HCC after surgical resection. The main drawback of these studies is the lack of international validation. Of all the studies published, the report that probably has the greatest clinical relevance is by Nault et al.,<sup>98</sup> which analyzed the gene expression patterns of HCC and compared said expression patterns with the survival times of patients who had undergone surgical resection. In this study, the authors were able to identify a genetic signature of 5 genes that, in the multivariate analysis, was significantly associated with patient prognosis. What is most relevant about the study is that this genetic signature was validated in different cohorts of patients from different geographical areas (Europe, United States, as well as in Asian patients).

**Recommendation 22.** *The risk factors for recurrence after resection used to assess transplantation are the presence of microscopic vascular invasion or satellitosis.*

*Evidence/recommendation II2B*

### Direct Liver Transplantation

Given that the presence of microvascular invasion and/or satellitosis in the histological analysis of the surgical specimen correlates with early recurrence and a poor short-term prognosis, some groups have proposed evaluating the direct inclusion of patients on the liver transplant list once dissemination in the resected segment is known, before the onset of tumor recurrence, with good initial results.<sup>99,100</sup>

In this context, the group at the Hospital Clinic of Barcelona presented in 2004 their initial results after the application of this policy,<sup>100</sup> which they have recently updated.<sup>101</sup> The authors propose that, in patients with resected HCC and risk factors such as vascular invasion and satellitosis, initial liver transplant should be considered without waiting for tumor recurrence. In their 1995–2012 series of 85 resected patients who met transplant criteria, 37 were at high risk of recurrence and 17 received liver transplants: 10 before relapse and 7 with recurrence while on the waiting list. Out of the 10 patients without recurrence, in 3 there was already a tumor in the hepatectomy piece, but no patient had long-term tumor recurrence. Out of the 7 patients with relapse prior to transplantation, 2 had a long-term tumor recurrence. And, out of the 48 low-risk patients, 26 had a relapse, while only rescue transplants were possible in 11 patients, 2 of which relapsed in the long term. As for all the high-risk patients, the overall 5-year survival rate was 60.2% (n=37), and in patients who underwent transplantation, a clear benefit was observed between transplant patients and non-transplant patients (5-year survival 82.4% vs 38%). The authors verified that, although there are statistically significant differences between the patients with high-risk and low-risk HCC (in favor of the latter), these differences are lost in the patients finally transplanted, observing a clear benefit of the policy of transplantation in patients with high risk. It is important to note that all high-risk patients were evaluated for HBOT/TOH by ab initio criteria. However, only 17 patients were trans-

planted; most of those who were not transplanted presented recurrence of the tumor outside of the TOH criteria during the evaluation.<sup>101</sup>

In 2012, Fuks et al.<sup>99</sup> presented their results after applying a similar protocol. Out of 138 resected patients in whom rescue liver transplantation was considered, they compared the 22 patients without recurrence with the 39 patients who had recurrence within the Milan criteria and who underwent rescue transplantation. Overall, they found that the risk factors for predicting a relapse outside the Milan criteria were: presence of cirrhosis, diameter >3 cm, microscopic vascular invasion, satellitosis and a low degree of differentiation. The authors found that when 3 or more risk factors accumulated, the incidence of tumor recurrence soared and the likelihood of this occurring outside the Milan criteria also increased (100%), which would rule out a rescue transplant. They proposed, therefore, that patients resected with 3 or more risk criteria were considered for liver transplantation before the onset of tumor recurrence. In those patients with <3 risk factors, using rescue transplants is necessary and possible.

In France, Tribillon et al.<sup>102</sup> also recently analyzed the benefits of this policy of initial transplantation in patients at risk for tumor recurrence in a series of 121 patients <65 years resected by HCC. Criteria for a good prognosis were the absence of vascular invasion and the presence of HCC with a high degree of cell differentiation. In these patients, they performed rescue transplantation when the tumor recurrence occurred (48 patients, 40 of whom received transplants). The presence of microscopic vascular invasion and/or a low degree of differentiation were considered poor prognostic criteria. These patients were prescribed an initial liver transplant (63 patients, 60 of whom were transplanted). They verified that the initial transplant group obtained a better survival and a better disease-free survival with statistically significant differences. They also found that these advantages were lost when patients had already had tumor recurrence before transplantation. Therefore, they proposed that patients resected due to HCC within the Milan criteria with microscopic vascular invasion and/or poor grade or moderately differentiated should be indicated for direct transplantation. In the remainder, they proposed performing the rescue transplant if tumor recurrence occurs.

**Recommendation 23.** *Direct transplantation in patients with risk factors for recurrence after resection should offer a 5-year survival >70%.*

*Evidence/recommendation IIIC*

### **Is a Waiting Period Necessary to Consider Direct Transplantation?**

From the results of these studies it can therefore be inferred that, in patients resected for HCC within the Milan criteria whose surgical pieces showed factors for a poor prognosis for tumor recurrence (microscopic vascular invasion, satellitosis and low or moderate degree of differentiation) a transplant is a good option to propose at the onset before evidence of tumor recurrence, as this is associated with good mid- and long-term

survival rates. However, when considering whether there is a waiting period between resection and transplantation to better select patients and thereby minimize the risk of early recurrence, the evidence in the literature is practically non-existent. In 69 patients undergoing rescue liver transplantation, Lee et al.<sup>103</sup> observed a significant drop in disease-free survival (DFS) when this was performed in the first 8 months after resection (5-year survival around 80% vs 20% with a  $P < .001$ ), with an HR of 53.124. They also found that AFP >200–200 ng/mL (HR 52.6) and being outside the Milan criteria when performing the transplantation (HR 52.2) were prognostic factors. They established that patients with no risk factors had better DFS than when they had one or 2, and having one or 2 risk factors was better than having 3.

The Clinic<sup>101</sup> group also found in their experience with direct transplants that, within the high-risk group, 9 patients out of 28 had a relapse that prevented liver transplantation with an average time of 6.5 months; they also found that all patients with recurrence in the first 6 months could not be transplanted. Based on these results, they propose an arbitrary waiting period of 6 months to identify patients with poorer tumor behavior, in whom transplantation should be avoided.

**Recommendation 24.** *It is considered appropriate to include patients with risk factors for recurrence after resection on transplant waiting lists.*

*Evidence/recommendation IIIC*

**Recommendation 25.** *It is recommended not to transplant within 6 months of a resection and that each hospital should apply their prioritization in these patients to avoid excessively delaying transplantation.*

*Evidence/recommendation IIIC*

### **Rescue Transplantation**

Regarding rescue liver transplantation, when tumor relapse has already occurred, there are several reports published in the literature with varying patient numbers that describe an average survival of 29 months, with a mean DFS of 21.8 months and 5-year survival and DFS rates of 62% and 67%, respectively.<sup>104–106</sup> These results are very comparable to direct liver transplants, so it seems an appropriate treatment option for patients who have undergone hepatic resection of an HCC and who present a tumor recurrence within the Milan criteria.<sup>107,108</sup>

Rescue transplant experiences have also been published in resected patients exceeding the Milan criteria, and when they present a recurrence, they have been transplanted with good long-term results.<sup>109</sup>

The group from the University of Bologna<sup>110</sup> conducted a Markov analysis in which they concluded that rescue transplants offer no benefits over direct transplants in countries with a low proportion of patients with HCC on the waiting list. However, the loss of the life expectancy of patients with HCC is very small and could be counteracted by

the benefit of the rest of the patients on the waiting list. The balance between the damage caused to the resected patients and the benefit to patients on the list depends on the proportion of candidates with HCC, the percentage resected and the average waiting time for transplantation. In countries with a high incidence of HCC, a greater proportion of patients with HCC on the waiting list and/or a longer average waitlist time, the rescue transplant could offer a gain in life expectancy for the rest of the patients. If the 5-year survival is lower than 60%, liver resection should be the best strategy to adopt.

**Recommendation 26.** *It is essential to prospectively analyze the results by applying this strategy to be able to evaluate its utility.*

#### Evidence/recommendation IIIIC

Limits of simultaneous liver–kidney transplantation:

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#### 1. Limits of elective liver retransplantation

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Fernando Pardo and José Antonio Pons have reviewed the manuscript. Lluís Castells, Jordi Colmenero, Miguel Ángel Gómez, Laura Lladó, Baltasar Pérez and Martín Prieto have contributed in the coordination of the group and composition of the recommendations. Javier Briceño has coordinated the groups, the document and its composition.

This present manuscript has been created and reviewed by the following experts from each of the 24 liver transplantation teams in Spain.

#### Conflict of Interests

The authors have no conflict of interests to declare.

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