Introduction

Hepatocellular cancer (HCC) is the fifth most common cancer and the second most frequent cause of tumour-related death, representing one of the major global health problems (1). As a consequence, HCC management is a topic of ongoing debate. In 2000, the European Association for the Study of the Liver (EASL) proposed a diagnostic/therapeutic algorithm internationally recognised as a useful protocol for the HCC management (2). According to this algorithm, liver resection (LR) represented one of the few therapeutic interventions identified for the treatment of HCC-on-cirrhosis. However, only an “ideal patient” was considered suitable for such an approach. Specifically, the EASL 2000 Guidelines defined the following criteria for LR:

- A solitary small (<2.0 cm) tumour;
- Very well-preserved liver function (i.e., Child-Pugh A status and bilirubin <2.5 mg/dL);
- Absence of portal hypertension (PHT) (i.e., hepatic vein-to-portal system gradient \(\leq 10\) mmHg or platelet count \(\geq 100,000/\text{mL}\));
- Performance Status (PST) zero.

In recent years, great evolutions have been observed in the management of HCC, pushing on the “old barriers” proposed by the EASL 2000 Guidelines. As an example, a large revision of the EASL Guidelines has been done in 2018 (1). The EASL 2018 Guidelines confirmed the previous concept of “ideal patient”, especially in the case...
of LR performed in non-experienced centres. However, the more recent guidelines underlined the fact that LR patients should present excellent results also in the presence of one or more risk factors when the resection is done in experienced centres (1,3-5). Such a shred of evidence has been the direct consequence of an accurate balance of the relative weight of each prognosis determinant. Interestingly enough, patients with risk factors can achieve excellent survivals after LR even if the more recent guidelines continue to direct them only towards alternative palliative treatments (1,3-5).

As a consequence, the present review aims at investigating the specific role of LR in the setting of HCC. We intend to report the studies able to demonstrate that LR is no longer a treatment suitable only for highly selected patients, but also for patients selectively presenting one-to-more negative factors. The following specific variables have been intensely investigated: age; single vs. multiple diseases; the dimension of the nodule; hyperbilirubinemia; clinically relevant PHT; Child-Pugh status; macrovascular invasion; laparoscopic approach.

The concept of age

Progressive ageing of the population is observed in several Western and Eastern countries. However, this progressive age increase does not represent an absolute contraindication to surgical approaches. In the specific setting of LR for HCC, the first studies demonstrating the feasibility of LR in aged patients were first published in the nineties (5,6).

According to the EASL Guidelines, age does not represent a contraindication per se, if adequate PST and no significant co-morbidities are confirmed (1).

In particular, post-surgical survivals compared in age-matched LR groups suggested that this procedure can be safely offered in >70-year-old patients, being exposed to a smaller loss of their lifespan in comparison with their younger counterparts (1).

A study from Italy performed on 919 HCC-oncirrhosis consecutive patients undertaking LR showed that postoperative mortality and 3-year survival rates were similar among age quartiles (≤60, 60–66, 67–70 and >70 years) (7).

Borzio et al. reported that post-LR outcome was mostly influenced by liver function and tumour stage rather than by age. Interestingly, the contemporaneous presence of advanced age and tumour stage, requiring a more extensive resection, was connected with lower results even when performed in experienced high-volume centres (8). Studies coming from Japan, Korea, China and Taiwan confirmed these pieces of evidence also in an Eastern setting (9-12).

Tumor dimension and number of nodules

In the absence of other risk factors, an HCC presenting with multiple nodules or with a lesion overpassing 5.0 cm of maximum diameter is not an absolute contraindication for surgical intervention (13-27) (Table 1). In particular, an HCC meeting the Milan Criteria (≤3 nodules, each ≤3 cm in size) could be approached with LR, if eligibility for liver transplantation is suboptimal or excluded (1).

A study from Toronto showed that LR for multifocal lesions consented to achieve excellent overall survivals (3-year: 59%). Moreover, multifocality was not an independent risk factor for patient death or post-resection recurrence (13). Another study by Ishizawa et al. confirmed these results, with the presence of multiple tumours failing to be an independent risk factor for post-operative survival. Interestingly, in these series, LR showed to provide a survival benefit in patients with multiple tumours even in the presence of PHT (14).

Several studies have compared the post-LR results with the large span of therapeutic alternatives usually proposed for multifocal HCC (18-20). For example, LR achieved competitive survivals when compared with trans-arterial chemo-embolization (TACE) (18,19).

As for the dimension of the primary lesion, several studies demonstrated that survival benefit is observed also resecting large (>5.0 cm) tumours (21,22).

As an example, Vitale et al. examined 2,090 HCC patients treated with LR, loco-regional therapies, and best supportive care, always showing a net survival benefit in favour of LR across all the stages of tumour presentation (23).

Liver function

EASL 2018 Guidelines asserted that Child-Pugh stage remains the most practised method for measuring liver function. Child-Pugh stage A is considered the limit for performing a LR within safe limits. However, other more recent parameters such as the model for end-stage liver disease (MELD), indocyanine green (ICG) kinetics, fibrosis grade using a liver stiffness measurement (LSM), albumin/bilirubin ratio, and cholinesterase/bilirubin ratio, have shown a significant role in improving patient selection, especially in those with borderline liver function (1).

Several West and East experiences showed a significant risk of post-hepatectomy liver failure predicted by LSM above
Table 1 Impact of multifocality and dimension of the nodule on post-LR survival rates

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year, origin</th>
<th>No. patients</th>
<th>Number of tumors</th>
<th>MST (months)</th>
<th>3-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pawlik TM</td>
<td>(15)</td>
<td>2005, USA</td>
<td>300</td>
<td>&lt;3 cm</td>
<td>190</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥3 cm</td>
<td>110</td>
<td>14</td>
</tr>
<tr>
<td>Ng KK</td>
<td>(16)</td>
<td>2005, China</td>
<td>380</td>
<td>&lt;3 cm</td>
<td>308</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥3 cm</td>
<td>72</td>
<td>14</td>
</tr>
<tr>
<td>Ruzzenente A</td>
<td>(17)</td>
<td>2009, Italy</td>
<td>136</td>
<td>&lt;3 cm</td>
<td>130</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥3 cm</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Zhong JH</td>
<td>(18)</td>
<td>2013, China</td>
<td>257</td>
<td>&lt;3 cm</td>
<td>199</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥3 cm</td>
<td>58</td>
<td>NA</td>
</tr>
<tr>
<td>Poon RTP</td>
<td>(24)</td>
<td>2002, China</td>
<td>120</td>
<td>&lt;5 cm</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥5 cm</td>
<td>120</td>
<td>19</td>
</tr>
<tr>
<td>Mok KT</td>
<td>(25)</td>
<td>2003, Taiwan</td>
<td>56</td>
<td>&lt;5 cm</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥5 cm</td>
<td>56</td>
<td>16</td>
</tr>
<tr>
<td>Shah SA</td>
<td>(26)</td>
<td>2007, Canada</td>
<td>189</td>
<td>&lt;5 cm</td>
<td>165</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥5 cm</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>Yamashita Y</td>
<td>(27)</td>
<td>2011, Japan</td>
<td>53</td>
<td>&lt;5 cm</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥5 cm</td>
<td>53</td>
<td>NA</td>
</tr>
</tbody>
</table>

MST, median survival time; NA, not available.

12–15 kPa (28-30). Nishio et al. reported that LSM could also be used to estimate a safe liver remnant volume (31).

A retention rate of ICG at 15 minutes (ICGR15) can be measured at the bedside with non-invasive pulse dye densitometry devices. Various cut-offs of ICGR15 can be part of the decision making an algorithm for LR procedures in cirrhotic patients, limiting resection and segmentectomy to patients with ICGR15 below 20–25% and 30–35%, respectively (32).

As for the different Barcelona Clinic Liver Cancer (BCLC) classes, several studies demonstrated that the proposed classification failed to predict post-resection survivals. As an example, Torzilli et al. reported that qualified surgical centres must offer LR once technical feasibility and hepatic functional reserve allows the surgical approach. Specifically, half of the cases (n=1,034) undergoing LR in their series were found to be at a stage considered unsuitable for hepatectomy. Interestingly, when BCLC B–C patients were considered, post-LR 3-year overall survival rates were 62% concerning the expected survivals of 10–40% (33).

Vitale et al. performed an analysis on 2,090 HCC-on-cirrhosis cases, reporting that LR was associated with a significant net benefit over loco-regional treatments.
Surprisingly, the observed benefit was present not only in the early stage (BCLC A) but also in intermediate stages (B–C). Importantly, this benefit persisted after a robust adjustment for adverse factors, including clinically significant PHT (23).

These findings may radically change the prognostic evaluation and management of HCC patients, suggesting that the BCLC stage does not influence the prognostic impact of different therapeutic approaches, and that LR should be preferred when technically feasible and clinically appropriate. On the opposite, when a stratification for MELD score was done, a net survival benefit after LR was observed concerning the other therapies when the MELD was 6–9. On the opposite, in the case of MELD >9, the net survival benefit was negligible or negative (23).

**Clinically relevant PHT and hyperbilirubinemia**

Although clinically relevant PHT and hyperbilirubinemia are significant prognostic factors affecting survival in both surgical and medical patients with HCC-on-cirrhosis (14,34), their relevance as independent determinants of post-surgical outcomes has been questioned. As limited resection in patients with preserved liver function and moderate PHT/hyperbilirubinemia yields competitive survival outcomes, their role in the decision making for eligibility to resection of HCC should always be balanced with the extent of hepatectomy and liver function indicators, such as the MELD score and the availability and predicted effectiveness of alternative HCC therapies (1).

As reported by the ITA.LI.CA Group, LR may be extended to patients with either clinically significant PHT or slight hyperbilirubinemia (<2.0 mg/dL) without compromising outcomes. Median survivals were similar in patients with hyperbilirubinemia alone (125 months) or PHT alone (100 months) concerning ideal candidates (93 months). On the opposite, PHT + hyperbilirubinemia had a significantly worse prognosis (85 months) (35).

Roayaie et al. reported an international study based on 10,135 HCC patients treated worldwide, in which four different groups (ideal candidates resected, ideal candidates not resected, nonideal candidates resected and nonideal candidates not resected) were compared. PHT alone (presence of either varices, splenomegaly, or platelet count <100,000/IL) or total bilirubin >1.0 mg/dL alone were not associated with an appreciable decrease in survival after LR. However, the contemporaneous presence of both was detrimental. Thus, the study concluded that there might be modest room for expansion of the resection criteria. As an example, a slight expansion able to include moderate PHT cases (platelet count >50,000/IL, no ascites) would increase the pool of ideal candidates by approximately 60%. Similarly, an expansion able to include patients with mild elevation of bilirubin (<2 mg/dL) would allow for approximately 25% more patients to undergo resection without any loss in long-term outcome (36).

**Macro-vascular invasion**

According to the EASL 2018 guidelines, cases with HCC-related portal vein thrombosis (PVT) present an advanced stage not amenable to curative treatments (1). However, it is known that patient prognosis is directly affected by the extension of PVT, especially in the presence of elevated alpha-fetoprotein and large tumours. In fact, PVT can be graded as PV1 (segmentary), PV2 (secondary order branch), PV3 (first-order branch), and PV4 (main trunk/contralateral branch) (37).

Several studies investigated the role of PVT in terms of impact on survival rates after LR (Table 2) (23,33,36,38-54).

A propensity matched-cohorts analysis by the Liver Cancer Study Group of Japan demonstrated that LR should be considered as the gold-standard treatment, as long as the PVT is limited to grades PV1–3, the liver function is preserved, and a no-R2 resection is achievable (53). Similarly, an international study showed a remarkable prognosis after LR for patients with HCC and PVT (54).

The surgical indications for PVT invading the main trunk or contralateral branch (PV4) are controversial (55). In the Japanese experience, the survival benefit after LR in the PV4 group was not statistically significant, and the R2 resection rate was relatively high. Considering that complete resection is extremely difficult in PV4 patients, the surgical indication in these cases requires further investigation (54). Neoadjuvant and adjuvant treatment including sorafenib and radiotherapy together with LR may be a promising treatment strategy for PV4 patients (56).

Nonetheless, no prospective comparison of LR vs. systemic treatments or radioembolization has ever been reported. Thus, it is not clear if the remarkable survivals observed in resected PVT cases were related to a super-selection of the investigated population. Therefore, LR should be suggested only in no-PV4 extension. However, such an approach should be considered only as an option to
be tested within research settings, and not as a standard of practice (1).

**The role of laparoscopic surgery**

The first mini-invasive cholecystectomy was reported in 1987 (57). After this initial experience, the mini-invasive approach rapidly became a reality also in the setting of liver surgery. The first mini-invasive liver surgery (MILS) approaches were reported in 1996 (58,59). After the first pioneering MILS cases (60), several series reported structured case-series with results often favouring laparoscopy respect to open surgery (61-63). As reported in the Consensus Conferences of Louisville 2008, Morioka 2014 and Southampton 2017, growing evidence exists that MILS approach is feasible for a great number of liver diseases (64-66). As an example, today laparoscopy is considered the standard for performing a left lateral sectionectomy (67).

However, retrospective MILS studies showing better outcomes concerning open series should be interpreted with caution, because of the propensity to perform these interventions only in super-selected patients (1). Concerning size, several studies questioned the superiority of laparoscopic anatomical LR in HCC >2.0 cm (22,68-71). As for the liver function, limited resections conducted through laparoscopic/robotic techniques in large-volume centres should be performed in patients with borderline conditions (i.e., Child B7, moderate PHT, bilirubin <2.0 mg/dL) (72,73).

As reported by the Southampton Consensus guidelines, meta-analyses and large propensity score-matched studies...

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**Table 2 Impact of portal vein thrombosis on post-LR survival rates**

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref.</th>
<th>Year, origin</th>
<th>N. patients</th>
<th>Median survival (months)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu CC</td>
<td>(38)</td>
<td>2000, Taiwan</td>
<td>112</td>
<td>NA</td>
<td>27</td>
</tr>
<tr>
<td>Fan J</td>
<td>(39)</td>
<td>2003, China</td>
<td>83</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Fan J</td>
<td>(40)</td>
<td>2005, China</td>
<td>108</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Pawlik TM</td>
<td>(41)</td>
<td>2005, Asia, Europe, USA</td>
<td>102</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Chen XP</td>
<td>(42)</td>
<td>2006, China</td>
<td>438</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Zhou J</td>
<td>(43)</td>
<td>2006, China</td>
<td>381</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td>Ikai I</td>
<td>(44)</td>
<td>2006, Japan</td>
<td>78</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Minagawa M</td>
<td>(45)</td>
<td>2007, Japan</td>
<td>1,517</td>
<td>12–36</td>
<td>18–37</td>
</tr>
<tr>
<td>Liang LJ</td>
<td>(46)</td>
<td>2008, China</td>
<td>86</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Shi J</td>
<td>(47)</td>
<td>2010, China</td>
<td>406</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Chang WT</td>
<td>(48)</td>
<td>2012, Taiwan</td>
<td>160</td>
<td>NA</td>
<td>29</td>
</tr>
<tr>
<td>Huang J</td>
<td>(49)</td>
<td>2012, China</td>
<td>116</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Yang T</td>
<td>(50)</td>
<td>2012, China</td>
<td>511</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>Roayaie S</td>
<td>(51)</td>
<td>2013, USA</td>
<td>165</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Wang JH</td>
<td>(52)</td>
<td>2013, Taiwan</td>
<td>68</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Torzilli G</td>
<td>(33)</td>
<td>2013, Europe, USA, Asia</td>
<td>297</td>
<td>NA</td>
<td>38</td>
</tr>
<tr>
<td>Zhong JH</td>
<td>(53)</td>
<td>2014, China</td>
<td>248</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Vitale A</td>
<td>(23)</td>
<td>2014, Italy</td>
<td>42</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Kokudo T</td>
<td>(53)</td>
<td>2016, Japan</td>
<td>1,877 (CP-A)</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>216 (CP-B)</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Kokudo T</td>
<td>(54)</td>
<td>2017, Japan</td>
<td>651</td>
<td>54</td>
<td>44</td>
</tr>
</tbody>
</table>

LR, liver resection; NA, not available; CP, Child-Pugh.
Comparing open versus laparoscopic LR for HCC, MILS was associated with reduced blood loss, transfusion rate, postoperative ascites, liver failure and hospital stay with comparable operation times, disease-free margin, and recurrence rates (66,73,74). In a recent series, this evidence has also been confirmed in cases requiring a major resection (75). In case of minor resections, a laparoscopic approach was found to be the only independent factor able to reduce the complication rates in resected HCC patients.

According to the Southampton guidelines, subcategories of “high-risk” patients, such as the elderly and patients with high body mass index, were no longer considered as contraindications to LR (66). When comparing MILS performed in cirrhotic versus no-cirrhotic cases, no differences were observed regarding operative time, blood loss, intraoperative complications, hospital stay, and morbidity (76). On the opposite, a laparoscopic approach appears to reduce the incidence of postoperative ascites, liver failure, and overall morbidity (77,78).

Conclusions

LR for the treatment of HCC-on-cirrhosis is a safe and effective procedure not only in “ideal cases”, but also for selected patients presenting some of the well-known risk factors of poor clinical course. The presence of one or more of these factors does not represent an absolute contraindication for LR but such cases should be evaluated in the context of a multidisciplinary team. Further studies investigating the “borderline” cases are required, mainly looking at the possible decisive role of laparoscopy in this setting.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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