BJS Open, 2025, zraf034
https://doi.org/10.1093/bjsopen/zraf034
Review Article

Liver transplantation as a treatment for cancer: comprehensive review

Bobby V. M. Dasari[1,2,*], Pal-Dag Line[3], Gonzalo Sapisochin[4], Taizo Hibi[5], Prashant Bhangui[6], Karim J. Halazun[7], Shishir Shetty[2,8], Tahir Shah[8], Christian T. J. Magyar[9], Conor Donnelly[7] and Dev Chatterjee[10]

[1]Department of Liver Transplantation and HBP Surgery, Queen Elizabeth Hospital, Birmingham, UK
[2]Department of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
[3]Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway
[4]Department of Surgery, Multi-Organ Transplant Program, University Health Network, Toronto, Canada
[5]Department of Pediatric Surgery and Transplantation, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan
[6]Liver Transplantation and Hepatobiliary Surgery, Medanta Institute of Liver Transplantation and Regenerative Medicine, Medanta-The Medicity, Gurgaon (Delhi NCR), India
[7]Department of Liver Transplantation and Hepatobiliary Surgery, NYU Grossman School of Medicine, NYU Langone Health, New York, USA
[8]Department of Hepatology, Queen Elizabeth Hospital, Birmingham, UK
[9]Department of Abdominal Transplant & HBP Surgical Oncology, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada
[10]BRC Clinical Fellow Liver Medicine, University Hospitals of Birmingham, Birmingham, UK

Correspondence to: Bobby V. M. Dasari, Queen Elizabeth Hospital, University of Birmingham, Level 3, Nuffield House, Edgbaston, Birmingham B15 2TH, UK (e-mails: b.dasari@bham.ac.uk; bobby.dasari@yahoo.com; bobby.dasari@uhb.nhs.uk)

Abstract

Background: Liver transplantation for cancer indications has gained momentum in recent years. This review is intended to optimize the care setting of liver transplant candidates by highlighting current indications, technical aspects and barriers with available solutions to facilitate the guidance of available strategies for healthcare professionals in specialized centres.

Methods: A review of the most recent relevant literature was conducted for all the cancer indications of liver transplantation including colorectal cancer liver metastases, hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, neuroendocrine tumours, hepatocellular carcinoma and hepatic epitheloid haemangioendothelioma.

Results: Transplant benefit from the best available evidence, including SECA I, SECA II, TRANSMET studies for colorectal liver metastases, various preoperative protocols for cholangiocarcinoma patients, standard, extended selection criteria for hepatocellular carcinoma and neuroendocrine tumours, are discussed. Innovative approaches to deal with organ shortages, including machine-perfused deceased grafts, living donor liver transplantation and RAPID procedures, are also explored.

Conclusion: Cancer indications for liver transplantation are here to stay, and the selection criteria among all cancer groups are likely to evolve further with improved prognostication of tumour biology using adjuncts such as radiomics, cancer genomics, and circulating DNA and RNA status. International prospective registry-based studies could overcome the limitations of smaller patient cohorts and lack of level 1 evidence.

Introduction

Transplant oncology is the treatment of cancer through transplant medicine and surgery[1–5]. It encompasses four pillars:

- the evolution of multidisciplinary cancer care mainly utilizes transplantation to treat cancers;
- exploration of genomic mechanisms. Organ transplantation offers a unique opportunity for cancer material to be genomically analysed, which is not available in other disciplines of medicine;
- extension of the traditional margins of surgical oncology. In transplantation, we utilize surgical techniques unique to this field, which can be used to achieve R0 resection in patients with hepatobiliary malignancies; and
- elucidation of recognition of tumour and transplant immunology. With immunotherapy being the treatment of choice for certain liver cancers, it is essential to elucidate its use in the transplant setting and its balance with immunosuppression.

The principles of surgical oncology, resectability, operability, transplantability and curability are needed to perpetuate the conceptual evolution of transplant oncology. The definition of resectability is assigned to liver tumours that can be resected based on the assessment of tumour-related and surgery-related factors. Its definition remains ambiguous, not always objective and is confined to surgical expertise and judgement. For example, portal vein embolization, associating liver partition, portal vein embolization for staged hepatectomy and hepatic vein deprivation are all imperative strategies to induce future liver remnant hypertrophy; however, they are utilized under

Received: December 06, 2024. **Revised:** January 30, 2025. **Accepted:** February 07, 2025

centre-specific criteria. Likewise, extreme resections such as *ex vivo* liver resection and autotransplantation, ante-situm liver resection with hypothermic perfusion and meso-Rex shunt are performed only in specialized centres[6–11]. Operability refers to the relative risk of an intervention, as determined by the physiologic state and perioperative anaesthesiologic risk (patient-related factor). On an individual level, 'cure' means that the patient never experiences disease after treatment (for example recurrence-free survival at 5 years). However, on a population level, there are different definitions depending on the epidemiological models utilized (for example mortality rate returning to the general population mortality rate). The term transplantability refers to the national or institutional criteria for transplant listing, relying on risk parameters for waitlist dropout (including but not limited to death or disease progression), post-transplant mortality rate and donor organ availability. Overall, these aspects lead to ethical considerations regarding organ allocation to candidates who may benefit from prolonged survival yet have a risk of recurrence. In light of organ shortages and neoadjuvant treatment protocols potentially requiring time-sensitive planning, living donor liver transplantation (LDLT) has gained a pivotal role in transplant oncology. LDLT, in turn, is associated with considerations regarding donor safety and the recipient's needs.

Transplant benefit is defined as the gain offered by liver transplantation (LT) compared with the best alternative therapy (survival after LT minus survival with the best alternative treatment). The International Liver Transplantation Society (ILTS) Consensus guidelines on Transplant Oncology emphasized that transplant benefit should be one of the key parameters to be considered when defining optimal selection criteria for LT.

All of these characteristics are to be driven by disease- and patient-related factors. This contemporary comprehensive review is intended to optimize the care setting of LT candidates by highlighting current indications, technical aspects and barriers with available solutions to facilitate the guidance of available strategies for healthcare professionals in specialized centres.

Tumour-specific sections

Colorectal cancer liver metastases

Almost 50% of patients with colorectal cancer will develop metastatic disease, and the liver is the most often involved organ. Liver resection remains the only potential curative treatment option for colorectal liver metastasis (CRLM). The rates of resectability have improved over time with the introduction of efficient chemotherapy for downstaging and techniques like two-stage hepatectomy (TSH)[12], as well as liver augmentation techniques like portal vein embolization (PVE) or Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS)[13,14]. Nevertheless, for 75–80% of the patients with CRLM, the only treatment option remains palliative chemotherapy, with a 5-year overall survival rate of about 10%[15].

The first controlled 'proof of concept' SEcondary CAncer (SECA-I) trial to explore LT in non-resectable CRLM was published in 2013 and found an estimated overall survival (OS) of 95%, 68% and 60% at 1, 3 and 5 years respectively[16]. However, disease-free survival (DFS) was only 35% at 1 year. Still, most recurrences were slow-growing lung metastases that could be offered curative intent resection, thereby yielding a favourable overall survival despite recurrence post-transplant. Risk factors for inferior survival were maximal tumour diameter >5.5 cm, time from primary cancer surgery <2 years, CEA levels >80 μg/l and disease progression after chemotherapy at the time of LT. The four factors constitute the 'Oslo-Score' by assigning 1 point to each for risk stratification. The 10-year outcome data of the SECA-I trial was published in 2022 and showed that a low Oslo score of 0–1 is associated with a 5-year and 10-year actual OS of 75 and 50% respectively[17].

In a follow-up study (SECA-II), the Oslo score factors were considered in the design of the inclusion criteria but were not applied directly. The study cohort, following more stringent inclusion criteria, resulted in Oslo scores of 02, and the estimated 1-, 3- and 5-year OS was 100%, 83% and 83% respectively[18]. Median DFS was 53%, 44% and 35% at 1, 2 and 3 years respectively and about 70% of the recurrences observed were lung metastases where a majority could be offered resection. The OS after recurrence was 100%, 73% and 73% at 1, 2 and 4 years respectively, indicating the DFS has limitations as a parameter of treatment efficacy in liver transplantation for CRLM.

As in all transplant oncology indications, patient selection remains critical to obtain acceptable outcomes and avoid futile use of grafts. The Oslo score alone is insufficient to suggest transplant candidacy; instead, a range of other negative predictive factors should be avoided[19]. CRLM in patients with right-sided primary tumours are associated with worse outcomes after chemotherapy, liver resection and liver transplantation[20–22], and BRAF mutation and undifferentiated or signet ring cell differentiation are similarly associated with inferior prognosis[23]. Examination with fluorine-18-fluorodeoxyglucose (F-FDG) PET/CT is commonly used to rule out extrahepatic disease. A metabolic tumour volume (MTV) on pretransplant PET/CT $<70\,cm^3$ is highly predictive of good survival outcomes after liver transplantation for CRLM and should be a routine part of the selection strategy[24–27].

A recent randomized clinical trial, TransMet, has compared liver transplantation + chemotherapy to chemotherapy alone in patients with unresectable CRLM[28]. The study population had a high tumour load with a median of 20 metastases in both groups, and the delay from diagnosis to randomization was 15.9 months in the transplant arm. All transplanted patients but one had a low Oslo-score (<2). After a median follow-up of 59.3 months, the 5-year intention-to-treat survival in the LT cohort was 56.6% in the transplant group compared with 12.6% in the chemotherapy group. In per-protocol analysis, the corresponding 5-year survival rates were 73.3% and 9.3%. The outcomes of the TRANSMET trial confirm the principal findings from all the previous clinical trials on LT for CRLM and have the potential to change clinical practice since CRLM is the only transplant oncology indication that is supported by level 1 evidence.

An increasing number of centres worldwide have started adopting LT for unresectable CRLM. Due to the scarcity of donor grafts in most countries and regions, many programmes have applied LDLT to be able to provide transplants to patients with CRLM, and the outcomes have largely been in line with other published results[29,30]. Systematic implementation of LDLT has, however, mostly been done in Asia, whereas the number of Western centres performing LDLT is limited. Split liver transplantation may offer a meaningful expansion of the donor pool, but the number of extra grafts obtained may be restricted by allocation policies in regions where MELD priority is used for

prioritization on the waiting list. In 2015, the RAPID concept (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy) was introduced as a possible method to provide liver transplantation for more patients with CRLM[31]. The RAPID procedure entails an auxiliary segment 2 + 3 transplantation after a left hepatectomy. After reperfusion, the portal flow is diverted to the graft under portal pressure guidance to induce fast liver generation. Graft size is monitored weekly, and the second-stage hepatectomy can usually be performed 2–3 weeks post-transplant. A multicentre study among seven European centres has demonstrated that the RAPID procedure may be applied with adequate safety, good functional liver regeneration and second-stage hepatectomy after a median of 2 weeks[32]. Moreover, RAPID can be applied both as a split liver technique in the deceased donor setting as well as with the use of living liver donors[33,34]. The latter is particularly attractive, since it possibly allows for a reduction in living donor risk whilst simultaneously offering a substantial treatment benefit for the CRLM recipient according to the double equipoise principle[35]. Since patients with CRLM usually do not have portal hypertension or liver failure, they generally may tolerate lower graft size than conventional liver transplant recipients with chronic liver disease. Thus, using smaller grafts, including living donor grafts, is a possible way to expand the donor pool and accommodate the increased need for liver grafts that liver transplantation for CRLM is likely to require in the future[36].

Hilar cholangiocarcinoma

Liver transplantation for unresectable hilar cholangiocarcinoma (hCCA) is not a new concept. In fact, the first transplant for this disease was performed by Thomas Starzl in 1963[37]. A total of eight patients with Klatskin tumours were transplanted by Starzl's group up until the mid-1980s, five of whom survived more than 2 months. Of those, 4 of 5 (80%) recurred and succumbed to their tumours; the single patient who did not recur died at the 2-month mark[38]. Similar to other early experiences with the transplantation of patients with malignancies, the abysmal outcomes observed in these initial series and experiences with transplantation of hilar cholangiocarcinoma resulted in the near abandonment of the use of liver transplant as a potential cure for this disease[38–41]. These poor outcomes can be attributed to poor patient selection and a lack of availability or adherence to strict chemotherapeutic protocols before transplantation. The Mayo protocol came into existence in 2000[42], and presented a group of patients who underwent chemoradiation using a protocol that involved combined 5-Fluorouracil (5-FU) with radiation. The results showed a median survival of 44 months and a single recurrence among 11 patients transplanted[42]. In 2004, Heimbach *et al.* published a follow-up on the original Mayo study that included 28 patients with hilar cholangiocarcinoma who underwent liver transplantation with an 82% 5-year OS and a 14.2% recurrence rate[43]. These excellent results propelled liver transplantation for hCCA through the establishment of the Mayo protocol.

Patient selection

The Mayo protocol has formed the basis of patient selection for unresectable hCCA since their updated results were published in 2006. Briefly, in order to qualify for a liver transplant, patients must have an unresectable tumour diagnosis which is established through brush cytology, the tumour must be under 3 cm in size and/or the patient has a malignant appearing stricture with a CA19-9 > 100 U/ml, and they must not have had a previous surgical exploration or a direct percutaneous/transperitoneal biopsy. The diagnosis in and of itself is often challenging to establish due to the unreliability or lack of sensitivity of brush cytology and biliary aspirates[44]. The diagnostic accuracy of cytologic brushings can be augmented with the addition of fluorescence *in situ* hybridization (FISH) to detect aneuploidy[45]. Often, however, multiple attempts at proving the diagnosis are made, causing delays in the commencement of therapies, and the presence of a mass in the hilum causing biliary obstruction with atypical cells on cytology can be sufficient (institutionally) to allow for inclusion into the protocol and commencement of neoadjuvant therapies. First, however, extrahepatic disease must be excluded—and hilar cholangiocarcinoma commonly metastasizes to regional lymph nodes, which should be sampled before inclusion. Routine endoscopic ultrasound (EUS)-guided biopsy of nodes should be performed before the commencement of chemoradiation to confirm the absence of metastases. Metastases to nodes and to any sites are an absolute contraindication to transplant. The United Network for Organ Sharing (UNOS) adopted the inclusion and exclusion criteria based on the Mayo protocol; these criteria are summarized in *Table 1*.

Neoadjuvant protocols

Neoadjuvant protocols have transformed the landscape of liver transplantation for hCCA, where complete surgical resection is often challenging. The rationale behind this regimen is to downstage tumours, enhance the probability of complete tumour eradication and limit recurrence post-transplantation[46]. Additionally, new agent therapy provides a biologic test, as more aggressive behaving tumours that progress despite treatment likely would not benefit from transplantation[47]. The original chemoradiation Mayo protocol involved the delivery of high-dose external beam radiation (EBRT) in combination with 5-FU for radio-sensitization as daily boluses for 3 weeks, followed by transcatheter radiation into the bile duct, followed by maintenance capecitabine until transplantation[43,48]. Centre-level variation in the dosage of radiation and the modality (SBRT *versus* EBRT) in which it is applied exist, with many centres avoiding brachytherapy and few altogether omitting radiation[49,50]. Chemotherapeutic regimens also vary,

Table 1 Inclusion and exclusion criteria for hilar cholangiocarcinoma

Inclusion criteria	Exclusion criteria
Unresectable hilar tumour mass ≤3 cm	Percutaneous or transperitoneal biopsy of tumour
Malignant stricture with one of: • CA19-9 > 100 U/ml without cholangitis • Cytology/biopsy determining malignancy, or • Aneuploidy/polyploidy by Fluorescence In Situ Hybridization (FISH)	Previous attempt at resection of the tumour (open cholecystectomy alone excluded)
Negative nodes by EUS before chemoradiation	Intrahepatic or extrahepatic metastases or positive nodes on EUS
Negative nodes on laparotomy/laparoscopy before transplant	

with some using gemcitabine instead of capecitabine, often in addition to cisplatin, based on the ABC-02 study[50,51]. Maintenance capecitabine is then usually given for maintenance chemotherapy during the transplant waiting interval, but some programmes report the use of gemcitabine with or without cisplatin[47,52].

Contrary to hepatocellular carcinoma, immunotherapy in cholangiocarcinoma has been utilized only in unresectable diseases, although studies have shown promising results for its use in systemic therapy and chemotherapeutic agents. In 2022, Oh *et al*. noted that durvalumab (PDL-1 antibody) plus gemcitabine-cisplatin significantly improved survival compared with gemcitabine-cisplatin plus placebo in advanced biliary tract cancer[53]. An RCT in 2023 showed improved OS for patients receiving pembrolizumab in combination with gemcitabine-cisplatin compared with gemcitabine-cisplatin alone for patients with advanced biliary tract cancer[54]. While this has not become standard practice, since none of these patients will be able to get immunotherapy after transplant due to the risk of rejection and severe complications resulting from immunosuppression, it seems reasonable to include immunotherapy in the neoadjuvant protocols for hilar cholangiocarcinoma.

Surgical protocol

Before undergoing transplantation, patients must undergo a complete sampling of the lymph nodes in the hilum of the liver and around the porta hepatis, specifically the common hepatic artery lymph nodes along the bile duct, and the portal vein nodes must be sampled. This can be performed through laparoscopic or robotic techniques, which minimize the amount of adhesions during the liver transplant procedure itself. Any positive nodes would preclude the patient from transplantation. Approximately 28% of patients with non-primary sclerosing cholangitis (PSC)-related hilar cholangiocarcinoma are found to have positive nodes or metastatic disease at the time of the staging operation[55]. The timing of the staging laparoscopy varies from centre to centre, with some choosing to perform the surgery immediately after the completion of neoadjuvant therapy or closer to the time of transplantation, and the availability of a living donor often influences the choice. Performing the staging operation shortly after completing neoadjuvant radiation provides more comprehensive information that allows precise listing decisions and mitigates the effects of radiation for easier dissection of the porta hepatis when there are fewer effects of radiation and cleaner planes. Postponing the staging operation until closer to the transplant date accounts for additional waiting time and a further assessment of the 'test of time' as it allows for the detection of metastatic disease that may have developed while waiting and, as outlined by Sonnendy[47], avoids the small risk of delays in listing due to complications from the staging procedure and reduces the chance of scar tissue and adhesions from the initial procedure complicating the portal dissection during transplantation[47]. There is no data to suggest, however, that the timing of the staging operation impacts the outcome.

The debate between LDLT and deceased donor liver transplant (DDLT) for hCCA revolves around access and surgical complexity. LDLT provides a guaranteed, quicker path to transplant. However, it comes with challenges, such as technical difficulties from shorter vessels requiring vascular anastomoses to previously radiated vessels for inflow. Avoidance of irradiated arteries in the DDLT setting is overcome by using vascular conduits from the deceased donor iliac artery to form an aortic conduit (supra-celiac or infrarenal)[56]. However, conduits are avoided during LDLT due to the risks of using third-party grafts. Although vascular complications are generally higher with LDLT, recent studies show acceptable risks postneoadjuvant radiation[57]. For DDLT, selecting a high-quality graft capable of tolerating longer cold ischaemia times is key, along with procuring suitable venous and arterial conduits for potential reconstruction. The recent rise in the use of machine perfusion, which mitigates cold ischaemic time issues, will likely allow the utilization of more marginal grafts in the DDLT setting for hCCA. Similarly, the radiation effect on the portal vein and the bile duct can cause significant scarring; however, the portal vein anastomosis is usually done in a standard fashion, with a Roux-en-Y performed for biliary reconstruction in all cases.

Post-transplant management

Post-transplant care for patients undergoing liver transplantation for hCCA follows standard protocols but requires heightened vigilance for technical complications, particularly due to the frequent need for vascular reconstructions. Vascular complications are a significant concern in hCCA transplant recipients. Early reports from the Mayo Clinic cited vascular complication rates as high as 40%, with some graft losses due to delayed hepatic artery thrombosis[58]. However, more recent studies indicate a lower rate of major vascular complications, closer to 20%, and fewer graft losses. A multicentre study from high-volume transplant centres reported a 90-day mortality rate of less than 5% in benchmark cases, comparable to or better than outcomes for other liver transplant indications[59]. Daily Doppler ultrasound surveillance is recommended for the first 3 to 7 days post-transplant[47]. Although therapeutic anticoagulation is not usually necessary, postoperative prophylactic anticoagulation and aspirin should be considered, especially in cases with arterial reconstructions. Drain placement should be monitored for biliary leaks and potential pancreatic injury from challenging portal dissections before removal[47]. Immunosuppression typically includes standard regimens (tacrolimus, mycophenolate mofetil and prednisone taper), as alternative mTOR inhibitor-based regimens (for example everolimus) have not shown definitive benefit in hCCA.

There is no clear evidence supporting the benefit of adjuvant chemotherapy post-transplantation, as studies, such as a European trial on adjuvant gemcitabine, have been inconclusive due to poor tolerance and lack of accrual[60]. Thus, chemotherapy is typically reserved for patients with recurrence or those with concerning explant pathology. Surveillance should follow protocols similar to those after hCCA resection, with contrast-enhanced cross-sectional imaging (magnetic resonance imaging (MRI) or computed tomography (CT)) of the abdomen and serum CA19-9 every 3 to 4 months for the first 3 years, then every 6 months for a total of 5 years. Annual chest CT is also recommended. While PET-CT is not routinely used, it may be added if there are suspicious findings or a rise in CA19-9[47].

Patient outcomes

It is difficult to assess the survival benefit of transplantation compared with alternative therapies, as the patients enrolled in these trials are a highly selected population. For example, the 5-year overall survival rate in the Mayo Clinic cohort exceeded 65%[57], with some studies reporting 5-year survival rates as high as 76% in highly selected populations[61]. Intent-to-treat protocols have shown lower survival, around 40–45%, suggesting high

levels of dropout in these patients due to progression or occult metastatic disease[47]. In a meta-analysis of studies comparing survival in these patients, the dropout ranged from 25.9% to 86.1%, with a 0% to 66.7% dropout of those who commenced chemoradiation therapy. In 41% of patients who discontinued therapy, dropout was related to disease progression—typically occurring at the time of the staging operation[62].

For those who have undergone transplantation, the median time to recurrence is around 2 years, with some recurrences occurring as late as 4 to 5 years post-transplant[63]. Risk factors for recurrence include perineural or vascular invasion, high tumour grade and nodal disease on explant, with twice the risk of recurrence in those with positive distal biliary margins following hepatectomy[45]. Recipients with PSC who underwent transplantation had half the risk of recurrence compared with those with *de novo* hCCA[64].

An initial comparison of resection to transplantation showed a significant survival advantage in those undergoing transplantation (5-year survival 82% *versus* 21%)[48]. Directly comparing the two groups is challenging for multiple reasons. In the aforementioned study, patients with PSC and inflammatory bowel disease were excluded from resection, and those undergoing transplantation were selected based on only those who had completed neoadjuvant chemoradiotherapy[48]. This comparison was reassessed in 2015, where a survival benefit was seen in patients with Bismuth–Corlette (B–C) IV but not B–C III disease in just those with *de novo* hCCA[65]. Importantly, cohorts including patients with PSC typically see a higher survival following transplantation, likely related to earlier diagnosis and more favourable tumour biology[61]. Highly selected patients with hCCA clearly have a benefit with liver transplantation, but determining the population that benefits is a complex problem.

Liver transplantation offers excellent outcomes in highly selected patients with unresectable hilar cholangiocarcinoma. The key to success is strict adherence to clinical protocols that include neoadjuvant chemoradiation. Patients with PSC have a more favourable outcome than those with *de novo* hCCA, and liver transplantation is the treatment of choice in such patients if they develop hCCA.

Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma (iCCA) accounts for less than 10% of primary liver cancer[66], with an incidence of 1.3 per 100 000 per year in Western countries. In Europe, 56% of all cholangiocarcinomas are iCCA[67]. The 2019 World Health Organization (WHO) classified iCCA into small-duct type and large-duct type[68]. Intrahepatic CCA can arise in both cirrhotic and non-cirrhotic patients and can occur as single or multifocal lesions. The predominant pattern of growth is mass forming in 93%, with positive regional lymph nodes in 50% and distant metastasis (predominantly lung, peritoneum or distant lymph nodes) in 24% of patients at the time of diagnosis[67]. The OS for all patients with iCCA is poor, with a 5-year OS of 14% and a median OS of 13 months respectively[69].

For iCCA, LT may be an option when the tumour is confined to the liver[70]. The two main indications for LT are: very early (≤2 cm) iCCA[71] in cirrhotic patients who are not resection candidates (that is end-stage liver disease, portal hypertension); and locally advanced (large or multiple with no macrovascular invasion, and no evidence of extrahepatic disease (cN0 cM0) iCCA that renders the disease not-resectable[70,72].

In non-cirrhotic patients with advanced iCCA, disease stability with neoadjuvant treatment is considered a selection criterion for transplantability by some advocates[70]. Special considerations are given to patients with primary sclerosing cholangitis[73]. Guidelines such as the EASL-ILCA and AASLD guidelines for managing CCA include transplant as an option for treatment management within trials[74,75].

A meta-analysis including studies up to May 2020 identified the pooled 5-year OS after LT as 42% (95% c.i. 29.0–55.0)[76]. Compared with non-transplant outcomes, good outcomes are reported in stage-stratified very early iCCA and advanced iCCA (5-year OS 71% *versus* 48%)[76]. The combination of LT with neoadjuvant treatment protocols has resulted in excellent results (5-year OS ranging up to 83.3%)[77,78]. The cumulative incidence of waitlist dropout at 12 months for cholangiocarcinoma patients is reported as 23.9% (95% c.i. 20.0–29.0)[79].

Whilst the gemcitabine-cisplatin-based neoadjuvant trial has proven effective[77], neoadjuvant protocols assessing immune checkpoint inhibitors (the first-line treatment option for advanced iCCA) are yet to be established. Currently, there is no consensus regarding the definition of transplant criteria in the context of neoadjuvant treatment. The MD Anderson-Methodist Transplant Center group reported radiological disease stability for 6 months under the neoadjuvant systemic therapy as a selection criterion for transplantation based on tumour biology in this setting[78].

Alternation from the standard of care for LT in the context of neoadjuvant treatment may vary on institutional and trial protocols. These may include a diagnostic laparoscopy to visually rule out peritoneal carcinomatosis and thorough portal lymph node dissection to rule out lymph node metastasis. As LDLT is a commonly employed transplantation of choice, the laparoscopy should be planned approximately 1 week before LT to allow for adequate histopathological examination (NCT 04195503)[80].

For post-transplant surveillance, the MD Anderson-Methodist Transplant Center proposed an imaging and biochemical follow-up every 3 months within the first 2 years, followed by 6 monthly intervals up to 5 years and thereafter annual follow-ups[78]. More recently, tissue and liquid biopsy (blood or bile) assessments for phenotyping and potential follow-up protocols have emerged[81–83]. Current molecular alterations of interest are FGFR2, IDH 1/2, NRG1, BRAF and BRCA. Incorporating liquid biopsy in treatment protocols is pivotal in allowing personalized medicine approaches for patients with iCCA in transplant oncology.

Neuroendocrine tumours

Neuroendocrine tumours (NETs) are rare cancers with a low incidence of only 0.5% of all malignancies[84,85]. However, the majority of patients present with or develop liver metastases during their lifetime, and these are often bilobar in distribution. Treatment options for neuroendocrine liver metastases (NELM) are variable, with most patients needing multimodal options of medical management with somatostatin inhibitors, surgical resection, systemic treatments, loco-regional options such as ablation and targeted treatment with radionuclide therapy. Surgical clearance of NELMs, even if it were to be debulking surgery, is accepted to prolong the survival and resolution of hormonal symptoms, especially in patients with functional NETs. Despite this, there is a subgroup of patients where the diffuse nature of intrahepatic metastases does not allow adequate debulking of liver lesions, and LT has been proposed as a curative option in such a situation.

Given the rare incidence and slow disease progression, high-quality data comparing the various treatment options is non-existent, and most of the evidence for surgical management of NELM is either from a retrospective registry or from single centres. Five-year survival rates from the European registry ranged from 47 to 70%, and cancer recurrence rates between 31.3 and 56.8%[86]. The European Liver Transplant Registry-based multicentre retrospective data showed a significantly better 5-year survival at 59% among patients transplanted after 2000 compared with 46% who underwent LT before 2000. Better results in the latter data are due to a improved patient selection with better understanding of poor prognostic factors that include presence of extrahepatic disease, resection of primary at the time of transplantation[21,42,87,88], vascular or nodal involvement[89].

The Milan Group in 2016 published outstanding 5-year and 10-year OS of 97 and 89% respectively, with liver transplantation for NELM[90,91]. Milan NET-LT criteria are, therefore, generally accepted as a standard in most programmes. These include low-grade NET (Ki67 index of less than 10%) regardless of function, a primary tumour with venous drainage via the portal system, which has been completely resected before transplantation, no more than 50% involvement of hepatic parenchyma, a responsive or stable disease for at least 6 months before transplantation and a recipient age of 55 years or younger (limit later increased to 60 years). The group has reported an adjusted transplant-related survival benefit of 6.82 months (95% c.i. 1.10–12.54; $P = 0.019$) and 38.43 months (95% c.i. 21.41–55.45; $P < 0.001$) at 5 and 10 years respectively.

Long-term outcomes were published in 2021[92], comparing the patients who underwent liver resection with curative intent and liver transplantation within the Milan criteria. Resection was offered to patients considered radically resectable and transplantation to unresectable. The 5-year and 10-year OS were 95 and 93% for transplant cohort, 90% and 75% for resection cohort ($P = 0.007$). The 5-year and 10-year DFS rates were 75 and 52% for LT and 33 and 18% for LR ($P < 0.001$). The median disease-free interval between liver surgery and recurrence was longer in the transplant cohort compared to resection cohort (78 *versus* 24 months, $P < 0.001$). Transplant patients showed a tendency for multisite recurrence, while resected patients for intrahepatic recurrence. This study might suggest that any patient with disease presentation meeting the Milan criteria may achieve a significant survival advantage with LT. A propensity score-matched study of resection *versus* transplantation for the patients within the Milan criteria demonstrated superior survival and disease control in the LT group with 88.8% 10-year OS and 13.1% disease progression compared with 22.4 and 89% respectively, in the resection group.

Challenges to transplantation for in NELMs include the continued debate about the selection of patients and the potential to expand the option to those patients with functional symptoms, higher tumour load and older patient cohorts. The most recent ENETS guidelines state that liver transplantation 'is an option in highly selected, preferably young patients, with functional syndromes, demonstrating early resistance to medical therapy'[93]. The role of 177lutetium-labelled peptide receptor radiotherapy as a competitor to transplnatation option and also in neoadjuvant settings will be of particular interest. With the availability of new and effective therapies, a prospective trial would be ideal for defining the role of transplantation in NET patients.

Hepatocellular cancer

Despite notable advancements in the management of patients with hepatocellular carcinoma (HCC) with respect to diagnosis, prognostication, treatment modalities available and posttreatment surveillance, there are yet unmet needs as regards the best curative treatment options in these patients to achieve long-term, recurrence-free survival. This is, of course, in addition to the significant problem of late detection of HCC at an advanced stage in most patients despite having screening protocols. Thus, achieving optimal outcomes in patients with HCC is still challenging.

It is known that close to 90% of HCCs occur in a diseased or cirrhotic liver; the aetiology of the underlying liver disease could be hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, ethanol, metabolic associated steatotic liver disease (MASLD) or others[94]. Unlike the other cancers managed in transplant oncology, the root cause of the development of HCC is the tumourigenic microenvironment provided by the cirrhotic liver. In addition, HCC by nature is a multicentric disease and pathology of explanted livers in patients with HCC reveals that 50–60% have multicentric tumours, of which at least 30% are unrecognized by pretransplant imaging. Any curative cancer surgery aims to try and obtain an R0 resection. Liver transplantation in well selected patients with HCC has the potential to cure the patient, with the extirpation of not only the tumour but also the underlying cirrhotic liver, which is responsible for the HCC arising in the first place. Hence, LT has been the modality with the best long-term outcomes in patients with HCC limited to the liver, with no macrovascular invasion. The key questions to answer are: when should LT be considered (choosing a strategy of ablation *versus* resection *versus* LT), how LT should be contemplated (which selection criteria should be followed and how far we can go when expanding transplant criteria) and in whom LT is expected to yield the best results.

Choosing the right strategy in early HCC: ablation versus resection versus LT

The Barcelona Clinic Liver Cancer (BCLC) staging and treatment criteria have been used in most parts of the world over the last three decades, with several modifications made to these criteria in the intervening interval[95–99]. For HCC in the very early stage (single ≤2 cm), ablation is the treatment of choice and radiofrequency or microwave ablation is known to achieve results similar to liver resection (LR) or LT. In tumours in the early stage according to the BCLC classification (single, or up to 3 nodules ≤3 cm, in patients with preserved liver function), resection or ablation may be offered to those with no clinically significant portal hypertension (CSPH) or those in whom LT is contraindicated. LT offers the best curative option in this group of patients especially those within the conventional criteria for LT (Milan criteria)[100] or the expanded and validated University of California San Francisco (UCSF) criteria[101].

One of the key questions in this group of patients is the proposed role of initial resection followed by LT in case of recurrence, the so-called salvage LT strategy[102]. However, series have shown that salvage LT is not an ideal strategy in these patients, since only 33% of patients who recur can actually have a curative LT on an intention-to-treat basis[103]. Hence, upfront LT would be associated with best results in patients with early HCC[104]. The other question is whether one modality fits the entire spectrum of very early and early patients with HCC. In patients with a single tumour up to 3 cm in size, published

evidence shows that resection could offer results similar to LT, and superior to ablation. However, in multiple tumours and tumours between 3 and 5 cm in size, LT is probably the best curative option[104]. If contraindicated or not feasible, in tumours up to 3 cm, a single ablation with radiofrequency or microwave ablation or transarterial chemoembolization (TACE) may be indicated. However, in tumours 3–5 cm in size, results with a combination of TACE and microwave ablation (MWA) are better than using a single modality. This has been elaborated on in the Indian National Association for Study of Liver (INASL)-modified BCLC classification where the early BCLC stage (Stage A) has been divided into Stages A1 and A2 and the treatment modality proposed accordingly[105]. Having said this, by far, the best results in patients with early-stage HCC are obtained with liver transplantation, and if feasible, transplantation should be offered to these patients.

The true dilemma: intermediate stage HCC (BCLC B)

Before the 2022 update of the BCLC staging system, patients with intermediate-stage HCC were relegated to receive non-curative systemic therapy alone. It is indeed rare for a physician, hepatologist or transplant surgeon to see a cirrhotic patient presenting with early HCC where multiple treatment options are available and feasible. Most present as multifocal and/or large tumours. The MASLD epidemic has further added to the late presentation, with large and biologically aggressive tumours[106]. These large and multifocal tumours, without extrahepatic disease or macrovascular invasion, could be considered locally advanced HCC. The pertinent question is whether some form of curative treatment can be offered to these patients.

Over the years, significant progress has been made in the prognostication of patients with HCC. The conventional criteria for LT (Milan and UCSF) based on size and number alone were found to be very restrictive. Patients with tumours beyond these transplant criteria were found to have similar OS, recurrence-free survival (RFS) and DFS if they were well selected based on tumour biology, and underwent LT. Some of the proposed expanded criteria are detailed in *Table 2* (DDLT)[107–114] and *Table 3* (LDLT)[115–121]. In the DDLT setting, large series (31 to 1556 patients) with expanded selection criteria for LT have reported acceptable long-term OS and DFS in patients with tumours up to 7.5 cm maximum diameter and up to three in number. The greatest push for expanding criteria has indeed come from the Asian countries where timely DDLT is not as feasible as it is in the West. If patients were to keep waiting for an organ, there is a high possibility that the patients with HCC would lose the chance to be transplanted due to the long waiting times. The main impetus in the selection criteria has been the absence of extrahepatic disease and gross vascular invasion and not so much on tumour size and number as in the conventional criteria.

The key is the use of tumour biology in the prediction of outcomes and, hence, in the selection of patients for transplant. The biological selection criteria incorporate tumour markers like alpha-fetoprotein (AFP), protein induced by vitamin-K absence-II (PIVKA) II (both as absolute value and a delta change), response to downstaging with loco-regional therapies, FDG-18 and Fibroblast activation protein inhibitor (FAPI)-PET avidity, waiting interval (as a test of time), inflammatory markers (such as neutrophil-lymphocyte ratio, platelet lymphocyte ratio) and sometimes histology (tumour differentiation) as surrogate markers to test tumour biology[122].

Successful downstaging (DS) can be an important tool for selecting patients beyond UCSF criteria for LT. Commonly used modalities for DS include TACE, TARE and focused radiotherapy. In fact, successful downstaging is a surrogate marker for favourable tumour biology as indicated by a decrease in tumour number and size as per RECIST criteria, serum AFP or PIVKA-II levels, loss of 18F-FDG PET CT avidity[123].

Biological criteria have been adopted by several centres and societies worldwide to demonstrate survival outcomes comparable to Milan/UCSF criteria. One such criterion classifies patients into low-, moderate- and high-risk groups and decides on upfront LDLT *versus* DS and then LDLT *versus* avoiding transplant respectively, based on morphological and biological prognostic markers[121]. There is a need for a comprehensive HCC-LT score able to offer a fair chance of justified transplantation to more patients with cirrhosis and HCC[122]. It was this exemplary work worldwide, across centres, that brought about a major change in the BCLC Staging in its 2022 update[99]. For the first time, LT found a place in the treatment of patients with intermediate-stage HCC. The guidelines now recommend LT in a select group of patients with HCC with BCLC Stage B tumours based on extended criteria which incorporate size and AFP levels. A novel concept called treatment stage migration (TSM) has been introduced in these guidelines, allowing for personalized treatment decisions based on clinical judgement when first-line treatment is not feasible due to patient characteristics. These updates emphasize the importance of individualized treatment approaches tailored to each patient's specific needs. The INASL-BCLC staging algorithm similarly differentiates between diffuse infiltrative bilobar disease and well differentiated nodules with the preserved portal flow to decide on TARE *versus* TACE/TARE ± SBRT or systemic therapy in non-transplantable patients[104].

Vitale *et al.* demonstrated that the highest survival benefit of LT is, in fact, in patients with HCC who have advanced liver cirrhosis and no extrahepatic disease (BCLC stage B, C) because there are no other effective alternative therapies for these patients[124]. Expanding criteria beyond Milan/UCSF (the conventional criteria) is indeed at the cost of 10–15% lower long-term survival, but the survival is significantly better in well selected cases compared with ablation or systemic therapy alone. In addition, several centres with extensive experience in LDLT have shown the benefit of a timely LDLT in well selected patients with HCC based on tumour biology and response to neoadjuvant or downstaging therapy. In our study, the transplant benefit at 5 years (as against local ablation with TACE or TARE) in patients who were classified as low risk for recurrence (based on a competing-risks regression model) was 42 months; it was 25 months even in those who were classified as high risk for recurrence[121].

HCC in a cirrhotic liver with tumoural portal vein thrombosis

It is an unfortunate fact that despite the surveillance programmes in place for high-risk cirrhotic patients, a significant proportion (10–40%) present with advanced stage HCC (with portal vein tumour thrombosis; PVTT) at the time of diagnosis; non-resectable, and non-transplantable according to the conventional criteria[99,125–127]. According to the BCLC algorithm, systemic therapy is proposed in these patients. If untreated, or in the case of palliative treatment alone, the outcome of these patients is poor, as shown by their short median (between 2 and 6 months) and 3-year survival (5%)[128,129]. The use of tyrosine kinase inhibitors (TKIs) in such patients yields poor median survival (OS of 5–19 months) according to most published series, and the time to tumour progression is short (4.1 months)[130]. One

Table 2 Some expanded criteria for hepatocellular cancer in the deceased donor liver transplantation setting

Criteria name, year	Criteria	No. of patients	OS/RFS using expanded criteria	Prognostic factors
Pamplona criteria, 2001[107]	1 nodule ≤ 6 cm or 2–3 nodules ≤5 cm	63, 12 beyond Milan	79% 5-year OS in entire group, 70% RFS	–
Mt. Sinai criteria, 2002[108]	≥ 1 nodule 5–7 cm (with neoadjuvant chemo + TACE)	31 in expanded criteria	55% 5-year OS in patients beyond Milan and within Mt. Sinai	–
Edmonton criteria, 2004[109]	1 nodule <7.5 cm, or any number <5 cm	40, 21 beyond Milan	83% 4-year OS and 77% RFS	Sirolimus helps in the beyond criteria cohort
UCSF criteria, 2001/2007[101]	Single tumour ≤ 6.5 or ≤3 nodules ≤ 4.5 and TTD ≤ 8 cm	168, 38 beyond Milan	75.2% 5-year OS, RFS 93%	–
UNOS Region 4, R4T3 criteria. 2007[110]	1 lesion <6 cm; ≤ 3 lesions, none >5 cm and total diameter ≤9 cm	445, 363 Milan and 82 expanded	77.1% 3-year OS, RFS 86.9%	–
Up to Seven, 2009[111]	Seven as sum of largest tumour diameter (cm) and no. of tumours	1556, 1112 beyond Milan	71.2% 5-year OS	MVI significantly affects survival
French AFP 2012[112]	AFP ≤100, > 100–1000, > 1000; largest diameter ≤3 cm, > 3–6 cm, > 6 cm; no. of nodules 1–3, ≥4	537 in test cohort, 435 for validation	OS / recurrence score ≤2: 67.8% ± 3.4% / 8.8% ± 1.7% Score >2: 47.5% ± 8.1% / 50.6% ± 10.2%	Incorporation of AFP in the model improves prediction of recurrence
Metro ticket 2.0 2018[113]	AFP <200, 200–400, 400–1000; sum of tumour size and number ≤7	1018 in training cohort, 341 for validation	70% 5-year OS: AFP <200, sum ≤7 AFP 200–400, sum ≤5 AFP 400–1000, sum ≤4	Outperformed Milan; UCSF; Shanghai-Fudan; up to 7 criteria and AFP French model to predict 5-year post-LT survival
NYCA 2018[114]	AFP response; tumour size 0–3, 3–6, > 6 cm; tumour number 1, 2–3, ≥4	1450, 235 outside Milan	OS: low risk: 75% acceptable risk: 62% high risk: 40% RFS: low risk: 90% acceptable risk: 70% high risk: 42%	AFP response consistently <200 ng/ml predicted the best outcome 201/ 235 patients outside Milan critrial recategorized into NYCA low/acceptable-risk groups

OS, overall survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing; MVI, microvascular invasion; AFP, alpha-fetoprotein; UCSF, University of California San Francisco; NYCA, New York/California; LT, liver transplantation.

Table 3 Some expanded criteria for hepatocellular cancer in the living donor liver transplantation setting

Criteria name, year	Criteria	No. of patients	OS/RFS using expanded criteria	Prognostic factors/comment
Tokyo (5-5 rule), 2007[115]	≤5 nodules and ≤5 cm	78	75% OS and 94% RFS at 5 years	–
Kyoto criteria, 2007[116]	≤10 nodules, all ≤5 cm and DGCP (PIVKA II) ≤ 400 mAU/ml	Total 136, 62 beyond Milan	87% OS and 5% RFS at 5 years	–
Asan criteria, 2008 (on explant path)[117]	Tumour diameter ≤ 5 cm, ≤ 6 lesions, no gross vascular invasion	221	82% OS at 5 years	Higher discriminatory power compared with Milan and UCSF
Kyushu criteria, Japan, 2009[118]	Any number of tumours, < 5 cm in size, PIVKA II <300	90, 54 beyond Milan	83% OS and 87% RFS at 5 years	Preop. DGCP ≥ 300 mAU/ml and tumour size ≥ 5 cm
Toronto criteria, 2011[119]	No number-size criteria. Poor tumour differentiation as exclusion	294	70% OS and 70% DFS at 5 years	–
Japanese National Expanded criteria 2019[120]	≤ 5 nodules and ≤5 cm, AFP <500 ng/ml	965, 301 beyond Milan	75.8% OS at 5 years	19% increase in the number of eligible patients
Medanta criteria, 2021[121]	No extrahepatic disease or major vascular invasion, irrespective of tumour size/number	405, 51% beyond Milan	64% OS and 70% RFS at 5 years	Prognostic model developed using a competing-risk RFS model to decide on upfront LDLT *versus* downstaging

OS, overall survival; RFS, recurrence-free survival; UCSF, University of California San Francisco; PIVKA, protein induced by vitamin-K absence-II; AFP, alpha-fetoprotein; DFS, disease-free survival; LDLT, living donor liver transplantation; DGCP, des-gamma carboxyprothrombin.

of the fallacies is presenting pooled data of these patients together with those patients who have distant metastases and extrahepatic spread (EHD)[131–133].

There have been published studies that have shown that upfront LDLT yields better survival compared with palliative or systemic therapy alone, especially in patients with segmental PVTT (first- and second-order portal venous branches), and those with low levels of AFP, low FDG-18 avidity on PET scan and small tumour sizes[134,135]. The results of LT have also been shown to be superior to resection in this context. Hence, PVTT in patients with HCC could be considered essentially a contiguous spread and thus a locally advanced tumour for an

interval of time before manifesting as a distant spread in a haematogenous fashion, and it may be pertinent to consider LT in a selected cohort of patients where the tumour biology is deemed favourable. It is, however, apt to note that the grade of PVTT is important, and the results of LT may not be similar in patients with segmental *versus* lobar or main PV tumour thrombosis[136,137].

Five-year OS and RFS of up to 53% and 52% respectively, have been reported using downstaging the tumour (especially ensuring that the PVTT is treated) using local ablation like TARE, SBRT and TACE, in combination with systemic therapy, and then going ahead with transplant once within institutional criteria[138].

It is true that the amount and quality of available evidence is limited, and it seems still too early to recommend LT in all patients with HCC with PVTT. One needs to be very wary when contemplating LT in patients with very high tumour marker levels or large infiltrative tumours and Vp4 tumour thrombus. It is also pertinent to note that the presence of concurrent hepatic vein tumour thrombosis (HVTT) heralds a very poor prognosis, and probably should be a relative contraindication for LT. In fact, HVTT can be considered more akin to a systemic disease.

Therefore, an individualized treatment plan within a multidisciplinary approach is important ideally in an intention-to-treat strategy. Surgery (resection and transplantation) still remains the only curative option in most patients, except those with very early HCC. As regards transplant for patients with cirrhosis with HCC, the ILTS transplant oncology guidelines consensus emphasized that selection criteria should consider tumour biology, size and number, probability of survival, transplant benefit, organ availability, waitlist composition and allocation priorities. Similarly, it was felt that composite criteria that consider surrogates of tumour biology and response to neoadjuvant treatments are likely to replace conventional morphological criteria for defining transplant feasibility.

Hepatic epithelioid haemangioendothelioma

Liver transplantation for unresectable hepatic epithelioid haemangioendothelioma (HEHE), is rarely performed. Five-year survival rates of 50–80% were reported from the USA and Europe, even in those patients with lymph node/extrahepatic metastases and macrovascular invasion[139–141]. Traditionally, HEHE diagnosis is difficult because of its disease rarity and similar microscopic appearance to other vascular malignancies; however, the diagnostic accuracy has greatly improved after the identification of two oncogenes, WW domain-containing transcription regulator 1 (*WWTR1*)–calmodulin binding transcription activator 1 (*CAMTA1*) or Yes-associated protein 1 (*YAP1*)–transcription factor E3 (*TFE3*) gene fusions that are found only in patients with HEHE[142,143].

In the USA, HEHE has become an indication for LT, with exception points from the National Liver Review Board in 2017[144]. A biopsy is mandatory to establish the diagnosis of HEHE and exclude haemangiosarcoma. The presence of extrahepatic disease is not an absolute contraindication. A retrospective cohort study conducted using a registry database from the United Network for Organ Sharing revealed that most HEHE recipients received exception points in the USA between 2002 and 2018, allowing prompt access to deceased donor LT. The unadjusted 5-year post-LT survival rate was 77.2% for 88 patients with HEHE, which did not differ significantly from that of patients with HCC but was superior to that of patients with cholangiocarcinoma or neuroendocrine tumour liver metastases[145]. Another study from the USA looked at >300 patients identified in the National Cancer Database who were treated for HEHE between 2004 and 2018 after the *WWTR1*–*CAMTA1* or YAP1–TFE3 gene fusion was discovered[146]. The 5-year post-LT overall survival rate ($n = 35$) was 62%, which was significantly better than the rates associated with any other modalities including non-surgical treatment, ablation or hepatic resection after adjusting for age, sex, race, type of health insurance, Deyo–Charlson Co-morbidity Index and tumour size (hazard ratio (HR) 0.61; 95% confidence interval (c.i.) 0.38–0.97). The authors proposed a treatment algorithm and recommended that LT is preferred for patients with multifocal and multilobar disease or patients at high risk of positive margins if treated with hepatic resections. Of note, living-donor LT for HEHE has also been reported[147–149].

Meanwhile, Lai *et al.* established a prognostic scoring system by analysing the outcomes of 149 recipients undergoing LT for HEHE between 1984 and 2014 in the ELTR-ELITA registry[150]. The 5-year post-LT OS and DFS rates were 79.5% and 79.4% respectively. The disease recurred in 37 (24.8%) patients after a median time of 18 months. Macrovascular invasion detected at pathology (HR 4.9; 95% c.i. 2.4–9.9), pre-LT waiting time ≤120 days (HR 2.5; 95% c.i. 1.2–5.3) and hilar lymph node invasion (HR 2.2; 95% c.i. 1.1–4.5) but not extrahepatic metastases, were found to be significant risk factors for post-LT recurrence. The HEHE-LT score was developed based on these three factors that successfully stratified the patients into three groups by their 5-year DFS rates: low score (0–2), 93.9% ($n = 58$), intermediate score (3–5), 76.9% ($n = 74$) and high score (6–10), 38.5% ($n = 17$). In 2020, the European Society for Medical Oncology (ESMO) held a virtual consensus meeting involving >80 experts to reach a global consensus on HEHE management[151]. This meeting concluded that LT for unresectable HEHE with no extrahepatic disease should be offered to patients 'after full disclosure of the potential benefits and the risks' associated with LT (level V evidence, Grade A recommendation).

History of tumour rupture was considered a major contraindication to LT. Several systemic treatments have been reported to be effective in further improving LT outcomes for HEHE. Early reports have shown promising results with neoadjuvant treatment with sirolimus (mammalian target of rapamycin) before LT and some reports confirmed the role of systemic therapy for recurrence following LT using tyrosine kinase inhibitors such as lenvatinib have also been described[152]. Further large-scale studies are essential to establish standardized LT criteria for unresectable HEHE and implement individualized multidisciplinary treatment to improve post-LT outcomes.

Effect of post-transplant immunosuppression on disease recurrence (lessons from HCC experience)

There has been significant interest in how immunosuppression required post-transplantation potentially has a role in cancer recurrence and whether specific protocols or regimens could prevent or delay recurrence, which has been better studied in patients who received LT for HCC.

Immunosuppression, required to limit graft failure through immune-mediated rejection, potentially provides an environment that facilitates tumour development and recurrence. It has been reported that there are cancers specifically associated with the immunosuppressed state including skin cancer, post-transplant lymphoproliferative disorder (PTLD), oesophageal carcinoma and genitourinary cancers. However, it is not clear cut as some forms of immunosuppression, including mTOR inhibitors (mTORi), have

been shown to disrupt the proliferation and support systems for cancer development and in clinical trials shown to have favourable results in several cancers, such as mantle cell lymphoma, endometrial carcinoma and renal cell carcinoma. This immunosuppression class-specific effect has been observed in HCC recurrence and will be described in the following section.

Calcineurin inhibitors (CNIs), such as cyclosporin and tacrolimus, have long been used in immunosuppressive regimens post-transplantation. CNIs have been shown to create an environment which enables tumour development and growth. For example, they increase the expression of transforming growth factor-β and vascular endothelial growth factor, both of which are known to promote HCC tumourigenesis[153,154]. Several studies have shown that high CNI exposure is an independent risk factor for HCC recurrence and reduced recurrence-free survival[155–157]. In these studies, high concentrations were defined as cyclosporin trough concentration of >300 ng/ml and tacrolimus trough concentration of >10 ng/ml. Further evidence of CNIs alone increasing HCC recurrence risk was shown in a large US retrospective cohort study with CNI monotherapy having a significantly increased risk compared with a combined CNI, antimetabolite and steroid immunosuppression regimen[158]. Furthermore, cumulative dose exposure to cyclosporin has been shown to increase HCC recurrence post-transplant and reduce 5-year recurrence-free survival, particularly when these higher doses are administered in the 4–12 month interval post-transplantation[156]. In contrast, these differences have only been observed in the first month with patients exposed to high-dose tacrolimus, with no significant difference noted after that[155,159]. The underlying reason for these differences between cyclosporin and tacrolimus is unclear and needs further assessment in larger prospective clinical trials.

In contrast to CNIs, mTORi, including sirolimus and everolimus, have antiangiogenic and antineoplastic effects by inhibiting the PI3K/Akt/mTOR pathway and reducing expression of vascular endothelial growth factor, resulting in reduced carcinogenesis[160–162]. Clinical studies comparing mTORi to tacrolimus-based immunosuppressive protocols showed statistically significant improved overall survival and reduced HCC recurrence in those receiving sirolimus[163–165]. This was also observed in studies in which cyclosporin or tacrolimus was used as the CNI agent, compared with sirolimus-only immunosuppression therapy[109,166]. It appears to be a potential class effect as similar significant differences in HCC recurrence and survival have been observed with everolimus compared with CNIs[167]. Furthermore, the combined sirolimus/CNI regimen had significantly improved recurrence-free survival up to 5 years compared with the CNI-only regimen, suggesting potential antagonism of the known procarcinogenic effects of CNI in HCC recurrence and antitumour advantage[166]. Interestingly, in a large retrospective registry-based cohort study, sirolimus survival benefit was greater in patients transplanted for HCC than patients without HCC, suggesting a specific benefit for the HCC cohort post-transplant[162]. In the only randomized clinical trial, recurrence-free survival and OS were noted up to 5 years post-transplantation, particularly in those with low risk of HCC recurrence, and the greatest recurrence-free survival and OS was noted in those patients on sirolimus monotherapy compared with combined immunosuppression regimens[168].

Further agents used for immunosuppression in liver transplantation, both for induction, acute rejection and maintenance, including corticosteroids, antimetabolites (for example azathioprine), anti-interleukin-2 receptor antibodies (ILR2a) and anti-thymoglobulin (ATG), have not been associated with HCC recurrence[155,156,158]. This has been demonstrated by the short- and long-term use of these agents in retrospective cohort studies.

Overall, mTORis are shown to independently improve HCC recurrence outcomes and development compared with CNI, with the greatest effect in patients with low risk of HCC recurrence. However, most studies covering the impact of immunosuppression on HCC recurrence have been retrospective cohort studies, and a single randomized clinical trial had a relatively low number of patients on mTOR monotherapy, preventing firm recommendations. Further prospective trials are therefore required to clarify the impact of immunosuppression in both induction and maintenance phases and their cumulative effect on HCC recurrence and outcomes, which will help guide clinical practice to optimize immunosuppressive regimens for these at-risk postliver transplant patients.

Organ shortage and use of marginal grafts

Organ shortage remains a challenge in most liver transplantation programmes worldwide. Individual centres have reported waitlist mortality rates as high as 20%. While the organ donation rates remain variable, with an increasing ageing population and higher incidence of metabolic co-morbidities such as diabetes mellitus and obesity, reduced quality of the grafts is increasingly encountered. Expanding the indications for liver transplantation for oncology patients could add to the existing demand, and the transplant community will need to continue exploring the options of expanding the donor pool based on the waitlists in their respective programmes.

Several attempts have been made to deal with the shortage and match the demand for the grafts, including the usage of donor after cardiac death (DCD) grafts and marginal donor after brain death (DBD) livers. The utilization of DCD grafts in Europe has increased significantly over the years[169]. Some countries, such as the UK, The Netherlands, Italy and Spain, were ahead of the rest, with well established frameworks and guidelines for DCD organ procurement and transplantation.

DCD grafts are at higher risk of ischmia reperfusion injury, primary non-function, delayed graft function, renal impairment, prolonged ICU stay and non-anastomotic biliary strictures than the DBD grafts[170,171]. The causation is multifactorial based on which the ILTS consensus outlined criteria for 'ideal' donors[172], including donor age ≤60 years, donor BMI ≤30 kg/m^2, macrovesicular steatosis <30% (in the absence of machine perfusion utilization) and cold ishemia time (CIT) <8 h. None of these factors is exclusive, and careful donor-recipient matching is needed to identify the suitable or at-need recipients for the higher-risk grafts. One important factor that determines the graft function of DCD grafts is the warm ischemic time (WIT), but the definitions and threshold for safe fWIT are variable. ILTS consensus guidelines recommend the definitions of total donor WIT as the withdrawal of treatment to cold flush, and functional donor (fDWIT) is the time point when either SpO_2 is <80% or mean arterial pressure is <60 mmHg until cold flush[172]. A maximum allowable time of 30 min of fDWIT is recommended by both the ILTS Consensus Conference and the UK DCD Risk Assessment[173]. Acceptable variations to all these criteria have been published. There have been successful reports of using DCD grafts from donors over 70 years[174,175]. Similarly, all other factors were also 'extended', usually with a balance between the CIT (<6 h), donor warm ischaemia time (WIT), recipient MELD scores and steatosis of the allograft[176].

Marginal DBD grafts refer to liver grafts obtained from DBD that are considered higher risk or 'marginal' due to various factors that may impact their function post-transplantation. These factors might include donor characteristics such as macrosteatosis, prolonged CIT and warm ischaemic times, elevated liver enzymes at liver offer, donor co-morbidities, cardiovascular instability and prolonged ICU stay. Marginal DBD grafts are also at risk of IRI, DGF and postoperative renal impairment[175]. Together with such risks and also due to ethical concerns, decline rates of livers as high as 50% have been reported[177].

However, advancements in organ preservation and assessment techniques have allowed to revisit these definitions. While no new standardized definitions of marginal grafts exist, the previously defined criteria are often overridden when the functional assessment criteria are supportive. Functional assessment of a liver on normothermic machine perfusion (NMP) allows for evaluating the viability (Birmingham, Cambridge, Groningen criteria) and function before transplantation and will enable logistics[178].

The VITTAL trial (Viability Testing in Transplants Aimed at Extended Life)[179] was a clinical study focused on exploring the use of normothermic machine perfusion (NMP) to assess the viability of livers from DCD, which is typically considered higher risk for transplantation. In this prospective, non-randomized, phase 2 trial, viability assessment with NMP allowed transplantation of 71% of discarded livers that were perfused with the intent of transplantation, with 100% 90-day patient and graft survival[180].

Hypothermic oxygenated perfusion (HOPE) in liver transplantation allows for improved outcomes in liver transplantation, particularly with marginal or donation after DCD grafts. During HOPE, the liver is perfused at a temperature of 4–10° C with an oxygenated solution. This process helps to recondition the liver, reduce cellular injury and enhance the removal of metabolic waste products that accumulate during warm ischaemia. The cooling slows down the metabolism, reducing the oxygen demand, while the oxygenated perfusion provides the necessary oxygen to maintain cellular integrity and repair mechanisms[181,182]. This reduces the oxidative stress associated with reperfusion once the liver is implanted. Studies demonstrated significantly lower rates of early allograft dysfunction and better overall graft function post-transplant, with a reduction in biliary complications[183]. Dual hypothermic oxygenated perfusion (D-HOPE) aims to optimize oxygen delivery to the liver cells (hepatocytes) and bile ducts (cholangiocytes), potentially reducing the risk of ischaemic injury more effectively than single vessel perfusion by perfusing the liver with oxygenated hypothermic saline both through the hepatic artery and portal vein. A European multicentre, randomized clinical trial on D-HOPE in regular DCD liver transplantation demonstrated a 64% reduction of non-anastomotic strictures (NAS), a 57% reduction in postreperfusion syndrome and a 39% reduction in early allograft dysfunction after transplantation[184]. This ultimately led to a Dutch prospective clinical trial by van Leeuwen *et al.* in which the authors evaluated sequential hypothermic and normothermic perfusion for declined livers to rewarm grafts in a controlled manner as their viability for transplantation was assessed[185].

The use of abdominal normothermic regional perfusion (NRP) aims to restore blood flow before organ recovery in an attempt to reverse the effects of warm ischaemia and improve outcomes. Experience from retrospective studies has shown reduced early allograft dysfunction and the risk of primary non-function compared with marginal DCD grafts, fewer overall biliary complications, graft loss and death compared with marginal DCD livers. Other studies have compared transplanted NRP livers with standard DBD liver outcomes and found them to be comparable[186].

All the perfusion modalities are the future (and present) of liver transplantation, allowing the use of marginal grafts and increasing donor graft utilization. Hence, machine perfusion programmes will undoubtedly facilitate the management of transplant oncology patients. The influence of machine perfusion modalities on cancer recurrence is not fully understood, although early data suggests reduced recurrence rates in the HCC cohort using HOPE[187]. Some centres have started moving to make transplant surgery a daytime procedure by utilizing the perfusion modalities[188]. Such flexibility in the logistics is beneficial in the field of transplant oncology, where frozen section evaluations are necessary.

Post-transplant follow-up

Post-transplant follow-up protocols should be aimed at detecting early recurrence, especially when they are oligometastases since they are amenable to directed therapy, which can significantly prolong survival[189]. Experienced units have shown that with the use of multimodality treatment, 1-year and 3-year OS of 57 and 24% respectively, was achieved, with a maximum postrecurrence survival of 7.5 years among post-LDLT patients with HCC recurrence[190]. It is, therefore, essential to have stringent follow-up protocols. In resource-constrained health systems, local protocols can be titred to those at higher risk of recurrence and for those beyond conventional criteria. One such example of post-LT follow-up protocol for patients with HCC is a CT scan (PET-CT if the tumour was initially FDG-18 PET avid) 6 monthly for 2 years and then yearly, ultrasound of the abdomen every 3 monthly for 2 years and then 6 monthly, and serum AFP and/or PIVKA-II levels 3 monthly for 2 years and then 6 monthly. SIMAP500, RECIST scores risk stratify the need for follow-up among patients with HCC, and similar strategies can be applied in the wider transplant oncology programmes[191].

In conclusion, cancer indications for liver transplantation are here to stay, while the selection criteria among all cancer groups are likely to evolve further with improved prognostication of tumour biology using adjuncts such as radionics, cancer genomics, and circulating DNA and RNA status. International prospective registry-based studies could overcome the limitations of small volumes and lack of level 1 evidence.

Funding

The authors have no funding to declare.

Disclosure

G.S.: grant support from Bayer®, Roche®; consultant for Novartis®, Integra®, Roche®, AstraZeneca®, Chiesi®, Eisai®, HepaRegeniX®, Stryker®; research collaborations with AstraZeneca®, HepaRegeniX®, Stryker®, Natera®. The authors declare no other conflict of interest.

Data availability

No new data were generated or analysed in support of this research.

Author contributions

Bobby Dasari (Conceptualization, Methodology, Project administration, Supervision, Writing—original draft, Writing—

review & editing), Pål Dag Line (Conceptualization, Formal analysis, Supervision, Writing—original draft, Writing—review & editing), Gonzalo Sapisochin (Methodology, Writing—original draft, Writing—review & editing), Taizo Hibi (Methodology, Writing—original draft, Writing—review & editing), Prashant Bhangui (Methodology, Writing—originial draft, Writing—review & editing), Karim J. Halazun (Methodology, Resources, Writing—original draft, Writing—review & editing), Shishir Shetty (Methodology, Writing—original draft, Writing—review & editing), Tahir Shah (Resources, Writing—review & editing), Christian T.J. Magyar (Writing—original draft), Conor Donnelly (Writing—original draft) and Devnandan Chatterjee (Methodology, Writing—original draft, Writing—review & editing).

References

1. Sapisochin G, Hibi T, Toso C, Man K, Berenguer M, Heimbach J *et al.* Transplant oncology in primary and metastatic liver tumors: principles, evidence, and opportunities. *Ann Surg* 2021;**273**:483–493
2. Krendl FJ, Bellotti R, Sapisochin G, Schaefer B, Tilg H, Scheidl S *et al.* Transplant oncology—current indications and strategies to advance the field. *JHEP Rep* 2023;**6**:100965
3. Hibi T, Sapisochin G. What is transplant oncology? *Surgery* 2019;**165**:281–285
4. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N *et al.* Liver transplantation for hepatocellular carcinoma. Working group report from the ILTS transplant oncology consensus conference. *Transplantation* 2020;**104**:1136–1142
5. Sapisochin G, Hibi T, Ghobrial M, Man K. The ILTS consensus conference on transplant oncology: setting the stage. *Transplantation* 2020;**104**:1119–1120
6. Yang X, Lu L, Zhu W-W, Tao Y-F, Shen C-H, Chen J-H *et al.* Ex vivo liver resection and auto-transplantation as an alternative for the treatment of liver malignancies: progress and challenges. *Hepatobiliary Pancreat Dis Int* 2024;**23**:117–122
7. Lopez-Lopez V, Linecker M, Caballero-Llanes A, Reese T, Oldhafer KJ, Hernandez-Alejandro R *et al.* Liver histology predicts liver regeneration and outcome in ALPPS. *Ann Surg* 2024;**279**:306–313
8. Conticchio M, Salloum C, Allard MA, Golse N, Pittau G, Ciacio O *et al.* The rex shunt for left portal vein reconstruction during hepatectomy for malignancy using of rex-shunt in adults for oncoliver surgery. *Surg Endosc* 2022;**36**:8249–8254
9. Nagino M, Hirano S, Yoshitomi H, Aoki T, Uesaka K, Unno M *et al.* Clinical practice guidelines for the management of biliary tract cancers 2019: the 3rd English edition. *J Hepatobiliary Pancreat Sci* 2021;**28**:26–54
10. Chebaro A, Buc E, Durin T, Chiche L, Brustia R, Didier A *et al.* Liver venous deprivation or associating liver partition and portal vein ligation for staged hepatectomy? *Ann Surg* 2021;**274**:874–880
11. Fard-Aghaie MH, Laengle J, Wagner KC, Reese T, Wirtz S, Oldhafer KJ. Liver surgery in the 2020s: ante-situm and in-situ resection are still indicated—a single-center study. *HPB* 2023;**25**:1030–1039
12. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann Surg* 2000;**232**:777–785
13. Sandstrom P, Røsok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G *et al.* ALPPS improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a scandinavian multicenter randomized controlled trial (LIGRO trial). *Ann Surg* 2018;**267**:833–840
14. Hemming A, Reed A, Howard R, Fujita S, Hochwald S, Caridi J *et al.* Preoperative portal vein embolization for extended hepatectomy. *Ann Surg* 2003;**237**:686–691. discussion 691–3
15. Cremolini C, Casagrande M, Loupakis F, Aprile G, Bergamo F, Masi G *et al.* Efficacy of FOLFOXIRI plus bevacizumab in liver-limited metastatic colorectal cancer: a pooled analysis of clinical studies by gruppo oncologico del nord ovest. *Eur J Cancer* 2017;**73**:74–84
16. Hagness M, Foss A, Line P-D, Scholz T, Jörgensen PF, Fosby B *et al.* Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 2013;**257**:800–806
17. Solheim JM, Dueland S, Line P-D, Hagness M. Transplantation for nonresectable colorectal liver metastases—long term follow-up of the first prospective pilot study. *Ann Surg* 2023;**278**:239–245
18. Dueland S, Syversveen T, Solheim JM, Solberg S, Grut H, Bjørnbeth BA *et al.* Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. *Ann Surg* 2020;**271**:212–218
19. Line P-D, Dueland S. Liver transplantation for secondary liver tumours: the difficult balance between survival and recurrence. *J Hepatol* 2020;**73**:1557–1562
20. Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M, Kitagawa Y. The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. *J Gastrointest Surg* 2016;**20**:648–655
21. Gasser E, Braunwarth E, Riedmann M, Cardini B, Fadinger N, Presl J *et al.* Primary tumour location affects survival after resection of colorectal liver metastases: a two-institutional cohort study with international validation, systematic meta-analysis and a clinical risk score. *PLoS One* 2019;**14**:e0217411
22. Smedman TM, Line P-D, Hagness M, Syversveen T, Grut H, Dueland S. Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (SECA-II arm D study). *BJS Open* 2020;**4**:467–477
23. Bonney GK, Chew CA, Lodge P, Hubbard J, Halazun KJ, Trunecka P *et al.* Liver transplantation for non-resectable colorectal liver metastases: the international hepato-pancreato-biliary association consensus guidelines. *Lancet Gastroenterol Hepatol* 2021;**6**:933–946
24. Dueland S, Smedman TM, Grut H, Syversveen T, Jørgensen LH, Line P-D. PET-uptake in liver metastases as method to predict tumor biological behavior in patients transplanted for colorectal liver metastases developing lung recurrence. *Cancers (Basel)* 2022;**14**:5042
25. Grut H, Line P-D, Syversveen T, Dueland S. Metabolic tumor volume from 18F-FDG PET/CT in combination with radiologic measurements to predict long-term survival following transplantation for colorectal liver metastases. *Cancers (Basel)* 2023;**16**:19
26. Grut H, Line P-D, Syversveen T, Dueland S. Metabolic tumor volume predicts long-term survival after transplantation for unresectable colorectal liver metastases: 15 years of experience from the SECA study. *Ann Nucl Med* 2022;**36**:1073–1081
27. Grut H, Dueland S, Line P-D, Revheim ME. The prognostic value of (18)F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. *Eur J Nucl Med Mol I* 2017;**4**:283
28. Adam R, Piedvache C, Chiche L, Adam JP, Salamé E, Bucur P *et al.* Liver transplantation plus chemotherapy versus

chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. *Lancet* 2024;**404**:1107–1118
29. Rajendran L, Claasen MP, McGilvray ID, Cattral MS, Ghanekar A, Selzner N *et al.* Toronto management of initially unresectable liver metastases from colorectal cancer in a living donor liver transplant program. *J Am Coll Surgeons* 2023;**237**:231–242
30. Hernandez-Alejandro R, Ruffolo LI, Sasaki K, Tomiyama K, Orloff MS, Pineda-Solis K *et al.* Recipient and donor outcomes after living-donor liver transplant for unresectable colorectal liver metastases. *JAMA Surg* 2022;**157**:524–530
31. Line P-D, Hagness M, Berstad AE, Foss A, Dueland S. A novel concept for partial liver transplantation in nonresectable colorectal liver metastases: the RAPID concept. *Ann Surg* 2015;**262**:e5–e9
32. Settmacher U, Ali-Deeb A, Coubeau L, Cillo U, Line P-D, Guba M *et al.* Auxilliary liver transplantation according to the RAPID procedure in non-cirrhotic patients—technical aspects and early outcomes. *Ann Surg* 2023;**277**:305–312
33. Königsrainer A, Templin S, Capobianco I, Königsrainer I, Bitzer M, Zender L *et al.* Paradigm shift in the management of irresectable colorectal liver metastases. *Ann Surg* 2019;**270**: 327–332
34. Rauchfuß F, Nadalin S, Königsrainer A, Settmacher U. Living donor liver transplantation with two-stage hepatectomy for patients with isolated, irresectable colorectal liver—the LIVER-T(W)O-HEAL study. *World J Surg Oncol* 2019;**17**:11
35. Pomfret EA, Lodge JPA, Villamil FG, Siegler M. Should we use living donor grafts for patients with hepatocellular carcinoma? Ethical considerations. *Liver Transplant* 2011;**17**:S128–S132
36. Cillo U, Furlanetto A, Gringeri E, Bertacco A, Marchini A, Rosso E *et al.* Advocating for a "shift-to-left" in transplant oncology: left grafts, RAPID and dual graft. *Updat Surg* 2024. Online ahead of print
37. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 1963;**117**:659–676
38. Iwatsuki S, Gordon RD, Shaw BW Jr, Starzl TE. Role of liver transplantation in cancer therapy. *Ann Surg* 1985;**202**:401–407
39. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surg* 1991;**110**:734–735
40. Goldstein RM, Stone M, Tillery GW. Is liver transplantation indicated for cholangiocarcinoma? *Am J Surg* 1993;**166**: 768–771; discussion 771–2
41. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000;**69**:1633–1637
42. De Vreede I, Steers JL, Burch PA *et al.* Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoradiation for cholangiocarcinoma. *Liver Transpl* 2000;**6**: 309–316
43. Heimbach JK, Haddock MG, Alberts S. Transplantation for hilar cholangiocarcinoma. *Liver Transpl* 2004;**10**:S65–S68
44. De Bellis M, Sherman S, Fogel EL *et al.* Tissue sampling at ERCP in suspected malignant biliary strictures (part 1). *Gastrointest Endosc* 2002;**56**:552–561
45. Moreno Luna LE, Kipp B, Halling KC *et al.* Advanced cytologic techniques for the detection of malignant pancreatobiliary strictures. *Gastroenterology* 2006;**131**:1064–1072
46. Akateh C, Ejaz AM, Pawlik TM, Cloyd JM. Neoadjuvant treatment strategies for intrahepatic cholangiocarcinoma. *World J Hepatol* 2020;**12**:693–708
47. Sonnenday CJ. Liver transplantation for hilar cholangiocarcinoma. *Surg Clin North Am* 2024;**104**:183–196
48. Rea DJ, Heimbach JK, Rosen CB. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005;**242**:451–458; discussion 458–61
49. Keltner SJ, Hallemeier C, Wang K. Neoadjuvant therapy regimens for hilar cholangiocarcinoma before liver transplant. *Am J Clin Oncol* 2023;**46**:276–278
50. Abdelrahim M, Esmail A, Xu J. Gemcitabine plus cisplatin versus non-gemcitabine and cisplatin regimens as neoadjuvant treatment for cholangiocarcinoma patients prior to liver transplantation: an institution experience. *Front Oncol* 2022;**12**:908687
51. Valle J, Wasan H, Palmer DH. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;**362**: 1273–1281
52. Rizzo A, Ricci AD, Cusmai A *et al.* Systemic treatment for metastatic biliary tract cancer: state of the art and a glimpse to the future. *Curr Oncol* 2022;**29**:551–564
53. Oh DY, Ruth He A, Qin S *et al.* Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evid* 2022;**1**:EVIDoa2200015
54. Kelley RK, Ueno M, Yoo C *et al.* Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023; **401**:1853–1865
55. Tan EK, Taner T, Heimbach JK, Gores GJ, Rosen CB. Liver transplantation for peri-hilar cholangiocarcinoma. *J Gastrointest Surg* 2020;**24**:2679–2685
56. McMillan RR, Saharia A, Abdelrahim M, Ghobrial RM. New breakthroughs for liver transplantation of cholangiocarcinoma. *Curr Transplant Rep* 2021;**8**:21–27
57. Darwish Murad S, Kim WR, Harnois DM *et al.* Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012;**143**:88–98.e3; quiz e14
58. Mantel HTJ, Rosen CB, Heimbach JK *et al.* Vascular complications after orthotopic liver transplantation after neoadjuvant therapy for hilar cholangiocarcinoma. *Liver Transpl* 2007;**13**:1372–1381
59. Breuer E, Mueller M, Doyle MB *et al.* Liver transplantation as a new standard of care in patients with perihilar cholangiocarcinoma? Results from an international benchmark study. *Ann Surg* 2022;**276**:846–853
60. Schmelzle M, Benzing C, Fischer L *et al.* Feasibility and efficacy of adjuvant chemotherapy with gemcitabine after liver transplantation for perihilar cholangiocarcinoma—a multi-center, randomized, controlled trial (pro-duct001). *Front Oncol* 2022;**12**:910871
61. Heimbach JK, Gores GJ, Haddock MG *et al.* Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation* 2006;**82**:1703–1707
62. Cambridge WA, Fairfield C, Powell JJ *et al.* Meta-analysis and meta-regression of survival after liver transplantation for unresectable perihilar cholangiocarcinoma. *Ann Surg* 2021; **273**:240–250
63. Machairas N, Kostakis ID, Tsilimigras DI, Prodromidou A, Moris D. Liver transplantation for hilar cholangiocarcinoma: a systematic review. *Transplant Rev* 2020;**34**:100516

64. Welling TH, Feng M, Wan S *et al.* Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. *Liver Transpl* 2014;**20**: 81–88
65. Croome KP, Rosen CB, Heimbach JK, Nagorney DM. Is liver transplantation appropriate for patients with potentially resectable de novo hilar cholangiocarcinoma? *J Am Coll Surg* 2015;**221**:130–139
66. Vithayathil M, Khan SA. Current epidemiology of cholangiocarcinoma in western countries. *J Hepatol* 2022;**77**: 1690–1698
67. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen H-J *et al.* Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA registry. *J Hepatol* 2022;**76**:1109–1121
68. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P *et al.* The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020;**76**:182–188
69. Xing H, Tan B, Yang C, Zhang M. Incidence trend and competing risk analysis of patients with intrahepatic cholangiocarcinoma: a population-based study. *Front Med (Lausanne)* 2022;**9**:1–16
70. Sapisochin G, Javle M, Lerut J, Ohtsuka M, Ghobrial M, Hibi T *et al.* Liver transplantation for cholangiocarcinoma and mixed hepatocellular cholangiocarcinoma: working group report from the ILTS transplant oncology consensus conference. *Transplantation* 2020;**104**:1125–1130
71. Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY *et al.* Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. *Hepatology* 2016; **64**:1178–1188
72. Sapisochin G, Ivanics T, Heimbach J. Liver transplantation for intrahepatic cholangiocarcinoma: ready for prime time? *Hepatology* 2022;**75**:455–472
73. Achurra P, Fernandes E, O'Kane G, Grant R, Cattral M, Sapisochin G. Liver transplantation for intrahepatic cholangiocarcinoma: who, when and how. *Curr Opin Organ Transplant* 2024;**29**:161–171
74. Alvaro D, Gores GJ, Walicki J, Hassan C, Sapisochin G, Komuta M *et al.* EASL-ILCA Clinical practice guidelines on the management of intrahepatic cholangiocarcinoma. *J Hepatol* 2023;**79**:181–208
75. Bowlus CL, Arrivé L, Bergquist A, Deneau M, Forman L, Ilyas SI *et al.* AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology* 2023;**77**:659–702
76. Ziogas IA, Giannis D, Economopoulos KP, Hayat MH, Montenovo MI, Matsuoka LK *et al.* Liver transplantation for intrahepatic cholangiocarcinoma: a meta-analysis and meta-regression of survival rates. *Transplantation* 2021;**105**:2263–2271
77. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N *et al.* Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 2018;**3**:337–348
78. McMillan RR, Javle M, Kodali S, Saharia A, Mobley C, Heyne K *et al.* Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. *Am J Transplant* 2022;**22**:823–832
79. Ziogas IA, Hickman LA, Matsuoka LK, Izzy M, Montenovo MI, Rega SA *et al.* Comparison of wait-list mortality between cholangiocarcinoma and hepatocellular carcinoma liver transplant candidates. *Liver Transplant* 2020;**26**:1112–1120
80. University Health Network. Liver transplant for stable, advanced intrahepatic cholangiocarcinoma; NCT04195503. clinicaltrials.gov. [cited 1 April 2024]. https://clinicaltrials.gov/study/NCT04195503 (accessed 15 February 2025)
81. Stenzinger A, Vogel A, Lehmann U, Lamarca A, Hofman P, Terracciano L *et al.* Molecular profiling in cholangiocarcinoma: a practical guide to next-generation sequencing. *Cancer Treat Rev* 2024;**122**:102649
82. Capuozzo M, Santorsola M, Ferrara F, Cinque C, Farace S, Patrone R *et al.* Intrahepatic cholangiocarcinoma biomarkers: towards early detection and personalized pharmacological treatments. *Mol Cell Probes* 2024;**73**:101951
83. Choi WJ, Williams PJ, Claasen MPAW, Ivanics T, Englesakis M, Gallinger S *et al.* Systematic review and meta-analysis of prognostic factors for early recurrence in intrahepatic cholangiocarcinoma after curative-intent resection. *Ann Surg Oncol* 2022;**29**:4337–4353
84. White BE, Rous B, Chandrakumaran K, Wong K, Bouvier C, Van Hemelrijck M et al. Incidence and survival of neuroendocrine neoplasia in England 1995-2018: a retrospective, population-based study. *Lancet Reg Health Eur*. 2022;**23**:100510
85. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y *et al.* Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017;**3**:1335–1342
86. Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S *et al.* Liver transplantation in patients with liver metastases from neuroendocrine tumors: a systematic review. *Surgery* 2017;**162**:525–536
87. Sher LS, Levi DM, Wecsler JS, Lo M, Petrovic LM, Groshen S *et al.* Liver transplantation for metastatic neuroendocrine tumors: outcomes and prognostic variables. *J Surg Oncol* 2015;**112**:125–132
88. Máthé Z, Tagkalos E, Paul A, Molmenti EP, Kóbori L, Fouzas I *et al.* Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. *Transplantation* 2011;**91**:575–582
89. Le Treut YP, Grégoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J *et al.* Liver transplantation for neuroendocrine tumors in Europe —results and trends in patient selection: a 213-case European liver transplant registry study. *Ann Surg* 2013;**257**:807–815
90. Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M *et al.* The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. *Am J Transplant* 2016; **16**:2892–2902
91. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007;**47**:460–466
92. Sposito C, Rossi RE, Monteleone M, Coppa J, Bongini M, Milione M *et al.* Postrecurrence survival after liver transplantation for liver metastases from neuroendocrine tumors. *Transplantation* 2021; **105**:2579–2586
93. Pavel M, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E *et al.* ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016; **103**:172–185
94. Ioannou GN, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2007;**5**: 938–945. 945.e1–4
95. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;**19**:329–338

96. Forner A, Reig M, Rodriguez De Lope C, Bruix J, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010;**30**:61–74
97. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;**379**:1245–1255
98. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018;**31**:1301–1314
99. Reig M, Forner A, Rimola J *et al.* BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2022;**76**:681–693
100. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;**334**:693–699
101. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A *et al.* Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;**33**:1394–1403
102. Fuks D, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. *Hepatology* 2012;**55**:132–140
103. Bhangui P, Allard MA, Vibert E *et al.* Salvage versus primary liver transplantation for early hepatocellular carcinoma: do both strategies yield similar outcomes? *Ann Surg* 2016;**264**:155–163
104. Adam R, Bhangui P, Vibert E *et al.* Resection or transplantation for early hepatocellular carcinoma in a cirrhotic liver: does size define the best oncological strategy? *Ann Surg* 2012;**256**:883–891
105. Kumar A, Acharya SK, Singh SP *et al.* 2023 update of Indian national association for study of the liver consensus on management of intermediate and advanced hepatocellular carcinoma: the puri III recommendations. *J Clin Exp Hepatol* 2024;**14**:101269
106. Koshy A. Evolving global etiology of hepatocellular carcinoma (HCC): insights and trends for 2024. *J Clin Exp Hepatol* 2025;**15**: 102406
107. Herrero JI, Sangro B, Quiroga J, Pardo F, Herraiz M, Cienfuegos JA *et al.* Influence of tumor characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. *Liver Transpl* 2001;**7**:631–636
108. Roayaie S, Frischer JS, Emre SH *et al.* Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002;**235**:533–539
109. Kneteman NM, Oberholzer J, Al Saghier M *et al.* Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. *Liver Transpl* 2004;**10**:1301–1311
110. Onaca N, Davis G, Goldstein RM, Jennings LW, Klintmalm GB. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the international registry of hepatic tumors in liver transplantation. *Liver Transpl* 2007;**13**:391–399
111. Mazzaferro V, Llovet JM, Miceli R *et al.* Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009;**10**:35–43
112. Duvoux C, Roudot-Thoraval F, Decaens T *et al.* Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012;**143**:986–994.e3; quiz e14–5
113. Mazzaferro V, Sposito C, Zhou J *et al.* Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2018;**154**: 128–139
114. Halazun KJ, Tabrizian P, Najjar M *et al.* Is it time to abandon the Milan criteria?: results of a bicoastal US collaboration to redefine hepatocellular carcinoma liver transplantation selection policies. *Ann Surg* 2018;**268**:690–699
115. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis* 2007;**25**:310–312
116. Takada Y, Ito T, Ueda M *et al.* Living donor liver transplantation for patients with HCC exceeding the Milan criteria: a proposal of expanded criteria. *Dig Dis* 2007;**25**:299–302
117. Lee SG, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB *et al.* Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl* 2008;**14**:935–945
118. Taketomi A, Sanefuji K, Soejima Y *et al.* Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. *Transplantation* 2009;**87**:531–537
119. Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A *et al.* The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. *Hepatology* 2016;**64**:2077–2088
120. Shimamura T, Akamatsu N, Fujiyoshi M *et al.* Expanded living-donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanese nationwide survey: the 5-5-500 rule—a retrospective study. *Transpl Int* 2019;**32**:356–368
121. Bhangui P, Saigal S, Gautam D *et al.* Incorporating tumor biology to predict hepatocellular carcinoma recurrence in patients undergoing living donor liver transplantation using expanded selection criteria. *Liver Transpl* 2021;**27**:209–221
122. Lerut PJ. Hepatocellualr cancer and liver transplantation: from the Tower of Babel towards a uniform language. *Transl Gastroenterol Hepatol* 2017;**2**:82
123. Cucchetti A, Serenari M, Sposito C, Di Sandro S, Mosconi C, Vicentin I *et al.* Including mRECIST in the Metroticket 2.0 criteria improves prediction of hepatocellular carcinoma-related death after liver transplant. *J Hepatol* 2020; **73**:342–348
124. Vitale A, Volk M, Cillo U. Transplant benefit for patients with hepatocellular carcinoma. *World J Gastroenterol* 2013;**19**: 9183–9188
125. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;**69**:182–236
126. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR *et al.* AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;**67**:358–380
127. Vogel A, Martinelli E, Guidelines Committee ESMO. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO clinical practice guidelines. *Ann Oncol* 2021;**32**:801–805
128. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006;**12**:7561–7567
129. Lee YH, Hsu CY, Huang YH, Hsia CY, Chiou YY, Su CW *et al.* Vascular invasion in hepatocellular carcinoma: prevalence, determinants and prognostic impact. *J Clin Gastroenterol* 2014; **48**:734–741
130. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A *et al.* Efficacy and safety of sorafenib in patients with advanced

hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012;**57**:821–829
131. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F *et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;**391**:1163–1173
132. Ricke J, Klümpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN *et al.* Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol* 2019;**71**:1164–1174
133. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY *et al.* Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;**382**:1894–1905
134. Lee KW, Suh SW, Choi Y, Jeong J, Yi NJ, Kim H *et al.* Macrovascular invasion is not an absolute contraindication for living donor liver transplantation. *Liver Transpl* 2017;**23**:19–27
135. Choi HJ, Kim DG, Na GH, Hong TH, Bae SH, You YK *et al.* The clinical outcomes of patients with portal vein tumor thrombi after living donor liver transplantation. *Liver Transpl* 2017;**23**:1023–1031
136. Cheng S, Chen M, Cai J; National Research Cooperative Group for Diagnosis and Treatment of Hepatocellular Carcinoma with Tumor Thrombus. Chinese expert consensus on multidisciplinary diagnosis and treatment of hepatocellular carcinoma with portal vein tumor thrombus: 2016 edition. *Oncotarget* 2017;**8**:8867–8876
137. Soin AS, Bhangui P, Kataria T, Baijal SS, Piplani T, Gautam D *et al.* Experience with LDLT in patients with hepatocellular carcinoma and portal vein tumor thrombosis postdownstaging. *Transplantation* 2020;**104**:2334–2345
138. Serenari M, Cappelli A, Cucchetti A, Mosconi C, Strigari L, Monari F *et al.* Deceased donor liver transplantation after radioembolization for hepatocellular carcinoma and portal vein tumoral thrombosis: a pilot study. *Liver Transpl* 2021;**27**:1758–1766
139. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P *et al.* Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. *Cancer* 2006;**107**:2108–2121
140. Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D *et al.* The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma: report of the European liver transplant registry. *Ann Surg* 2007;**246**:949–957
141. Rodriguez JA, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: the UNOS experience from 1987 to 2005. *J Gastrointest Surg* 2008;**12**:110–116
142. Mendlick MR, Nelson M, Pickering D, Johansson SL, Seemayer TA, Neff JR *et al.* Translocation t(1;3)(p36.3;q25) is a nonrandom aberration in epithelioid hemangioendothelioma. *Am J Surg Pathol* 2001;**25**:684–687
143. Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG *et al.* A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer* 2011;**50**:644–653
144. U.S. Department of Health & Human Services: Organ Procurement and Transplantation Network. Guidance to liver transplant programs and the national liver review board for adult MELD exception review. 2017. https://optn.transplant.hrsa.gov/resources/guidance/liver-review-board-guidance. (accessed 7 July 2024)
145. Brahmbhatt M, Prenner S, Bittermann T. Liver transplantation for hepatic epithelioid hemangioendothelioma is facilitated by exception points with acceptable long-term outcomes. *Transplantation* 2020;**104**:1187–1192
146. Kaltenmeier C, Stacchiotti S, Gronchi A, Sapisochin G, Liu H, Ashwat E *et al.* Treatment modalities and long-term outcomes of hepatic hemangioendothelioma in the United States. *HPB (Oxford)* 2022;**24**:1688–1696
147. Umeshita K, Eguchi S, Egawa H, Haga H, Kasahara M, Kokudo N *et al.* Liver transplantation in Japan: registry by the Japanese liver transplantation society. *Hepatol Res* 2019;**49**:964–980
148. Na BG, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY *et al.* Prognosis of hepatic epithelioid hemangioendothelioma after living donor liver transplantation. *Korean J Transplant* 2021;**35**:15–23
149. Fukuhara S, Tahara H, Hirata Y, Ono K, Hamaoka M, Shimizu S *et al.* Hepatic epithelioid hemangioendothelioma successfully treated with living donor liver transplantation: a case report and literature review. *Clin Case Rep* 2019;**8**:108–115
150. Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M *et al.* Hepatic epithelioid hemangioendothelioma and adult liver transplantation: proposal for a prognostic score based on the analysis of the ELTR-ELITA registry. *Transplantation* 2017;**101**:555–564
151. Stacchiotti S, Miah AB, Frezza AM, Messiou C, Morosi C, Caraceni A *et al.* Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. *ESMO Open* 2021;**6**:100170
152. di Francesco F, Di Lorenzo N, Gruttadauria S. Extra-hepatic epithelioid hemangioendothelioma: pushing the limit with sirolimus in combination with liver transplantation. *Updates Surg* 2024;**76**:2091–2092
153. Baba AB, Rah B, Bhat GR, Mushtaq I, Parveen S, Hassan R *et al.* Transforming growth factor-beta (TGF-β) signaling in cancer–a betrayal within. *Front Pharmacol* 2022;**13**:791272
154. Moawad AW, Szklaruk J, Lall C, Blair KJ, Kaseb AO, Kamath A *et al.* Angiogenesis in hepatocellular carcinoma; pathophysiology, targeted therapy, and role of imaging. *J Hepatocell Carcinoma* 2020;**7**:77–89
155. Rodríguez-Perálvarez M, Tsochatzis E, Naveas MC, Pieri G, García-Caparrós C, O'Beirne J *et al.* Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. *J Hepatol* 2013;**59**:1193–1199
156. Vivarelli M, Bellusci R, Cucchetti A, Cavrini G, De Ruvo N, Aden A *et al.* Low recurrence rate of hepatocellular carcinoma after liver transplantation: better patient selection of lower immunosuppression? *Transplantation* 2002;**74**:1746–1751
157. Vivarelli M, Dazzi A, Zanello M, Cucchetti A, Cescon M, Ravaioli M *et al.* Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. *Transplantation* 2010;**89**:227–231
158. Durkin C, Schaubel DE, Xu Y, Mahmud N, Kaplan DE, Abt PL *et al.* Induction immunosuppression does not worsen tumor recurrence after liver transplantation for hepatocellular carcinoma. *Transplantation* 2023;**107**:1524–1534
159. Kim DG, Yim SH, Min EK, Choi MC, Joo DJ, Kim MS *et al.* Cumulative exposure to tacrolimus during early period after liver transplantation does not affect the recurrence of hepatocellular carcinoma. *Sci Rep* 2023;**13**:20236
160. Ali ES, Mitra K, Akter S, Ramproshad S, Mondal B, Khan IN *et al.* Recent advances and limitations of mTOR inhibitors in the treatment of cancer. *Cancer Cell Int* 2022;**22**:284

161. Lerut J, Iesari S, Foguenne M, Lai Q. Hepatocellular cancer and recurrence after liver transplantation: what about the impact of immunosuppression? *Transl Gastroenterol Hepatol* 2017;**2**:80
162. Toso C, Merani S, Bigam DL, Shapiro AMJ, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010;**51**:1237–1243
163. Chinnakotla S, Davis GL, Vasani S, Kim P, Tomiyama K, Sanchez E *et al.* Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transplantation* 2009;**15**:1834–1842
164. Zhou J, Wang Z, Wu ZQ, Qiu SJ, Yu Y, Huang XW *et al.* Sirolimus-based immunosuppression therapy in liver transplantation for patients with hepatocellular carcinoma exceeding the Milan criteria. *Transplant Proc* 2008;**40**:3548–3553
165. Yang Z, Wang S, Tian XY, Xie QF, Zhuang L, Li QY *et al.* Impact of treatment modalities on patients with recurrent hepatocellular carcinoma after liver transplantation: preliminary experience. *Hepatobiliary Pancreat Dis Int* 2020;**19**:365–370
166. Zimmerman MA, Trotter JF, Wachs M, Bak T, Campsen J, Skibba A *et al.* Sirolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. *Liver Transplantation* 2008;**14**:633–638
167. Ferreiro AO, Vazquez-Millán MA, López FS, Gutiérrez MG, Diaz SP, Patiño MJL. Everolimus-based immunosuppression in patients with hepatocellular carcinoma at high risk of recurrence after liver transplantation: a case series. *Transplant Proc* 2014;**46**:3496–3501
168. Geissler EK, Schnitzbauer AA, Zölke C, Lamby PE, Proneth A, Duvoux C *et al.* Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. *Transplantation* 2016;**100**:116–125
169. Haque O, Yuan Q, Uygun K, Markmann JF. Evolving utilization of donation after circulatory death livers in liver transplantation: the day of DCD has come. *Clin Transplant* 2021;**35**:e14211
170. Leithead JA, Tariciotti L, Gunson B, Holt A, Isaac J, Mirza DF *et al.* Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. *Am J Transplant* 2012;**12**:965–975
171. Hilger B, Frick K, Erlebach R, Dutkowski P, Andermatt R, David S *et al.* Comparative study of acute kidney injury in liver transplantation: donation after circulatory death versus brain death. *Ann Transplant* 2024;**29**:e944077
172. Kalisvaart M, Croome KP, Hernandez-Alejandro R, Pirenne J, Cortés-Cerisuelo M, Miñambres E *et al.* Donor warm ischemia time in DCD liver transplantation-working group report from the ILTS DCD, liver preservation, and machine perfusion consensus conference. *Transplantation* 2021;**105**:1156–1164
173. Schlegel A, Muller X, Kalisvaart M, Muellhaupt B, Perera MTPR, Isaac JR *et al.* Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. *J Hepatol* 2019;**70**:50–57
174. Fallani G, Stocco A, Siniscalchi A, Antonini MV, Stella AP, Amato A *et al.* Beyond the concepts of elder and marginal in DCD liver transplantation: a prospective observational matched-cohort study in the Italian clinical setting. *Transpl Int* 2023;**36**:11697
175. Dasari BV, Mergental H, Isaac JR, Muiesan P, Mirza DF, Perera T. Systematic review and meta-analysis of liver transplantation using grafts from deceased donors aged over 70 years. *Clin Transplant* 2017;**31**
176. Laing RW, Scalera I, Isaac J, Mergental H, Mirza DF, Hodson J *et al.* Liver transplantation using grafts from donors after circulatory death: a propensity score-matched study from a single center. *Am J Transplant* 2016;**16**:1795–1804
177. Dobbins JJ, Tingle SJ, Mehew J, Thompson ER, Kourounis G, McPherson S *et al.* Impact of donor transaminases on liver transplant utilisation and unnecessary organ discard: national registry cohort study. *Front Transplant* 2024;**3**:1458996
178. Panconesi R, Flores Carvalho M, Mueller M, Meierhofer D, Dutkowski P, Muiesan P *et al.* Viability assessment in liver transplantation—what is the impact of dynamic organ preservation? *Biomedicines* 2021;**9**:161
179. Laing RW, Mergental H, Yap C, Kirkham A, Whilku M, Barton D *et al.* Viability testing and transplantation of marginal livers (VITTAL) using normothermic machine perfusion: study protocol for an open-label, non-randomised, prospective, single-arm trial. *BMJ Open* 2017;**7**:e017733
180. Mergental H, Laing RW, Kirkham AJ, Perera MTPR, Boteon YL, Attard J *et al.* Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun* 2020;**11**:2939
181. Muller X, Schlegel A, Würdinger M, Wendt M, Kron P, Eshmuminov D *et al.* Can hypothermic oxygenated perfusion (HOPE) rescue futile DCD liver grafts? *HPB (Oxford)* 2019;**21**:1156–1165
182. Eden J, Thorne AM, Bodewes SB, Patrono D, Roggio D, Breuer E *et al.* Assessment of liver graft quality during hypothermic oxygenated perfusion: the first international validation study. *J Hepatol* 2024;**82**:523–534
183. Schlegel A, Mueller M, Muller X, Eden J, Panconesi R, von Felten S *et al.* A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. *J Hepatol* 2023;**78**:783–793
184. van Rijn R, Schurink IJ, de Vries Y, van den Berg AP, Cortes Cerisuelo M, Darwish Murad S *et al.* Hypothermic machine perfusion in liver transplantation—a randomized trial. *N Engl J Med* 2021;**384**:1391–1401
185. van Leeuwen OB, Bodewes SB, Lantinga VA, Haring MPD, Thorne AM, Brüggenwirth IMA *et al.* Sequential hypothermic and normothermic machine perfusion enables safe transplantation of high-risk donor livers. *Am J Transplant* 2022;**22**:1658–1670
186. Hessheimer AJ, Coll E, Torres F, Ruíz P, Gastaca M, Rivas JI *et al.* Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* 2019;**70**:658–665
187. Mueller M, Kalisvaart M, O'Rourke J, Shetty S, Parente A, Muller X *et al.* Hypothermic oxygenated liver perfusion (HOPE) prevents tumor recurrence in liver transplantation from donation after circulatory death. *Ann Surg* 2020;**272**:759–765
188. Brüggenwirth IMA, Lantinga VA, Lascaris B, Thorne AM, Meerdink M, de Kleine RH *et al.* Prolonged hypothermic machine perfusion enables daytime liver transplantation—an IDEAL stage 2 prospective clinical trial. *EClinicalMedicine* 2024;**68**:102411
189. Au KP, Fung JYY, Dai WC, Chan ACY, Lo CM, Chok KSH. Verifying the benefits of radical treatment in posttransplant hepatocellular carcinoma oligo-recurrence: a propensity score analysis. *Liver Transpl* 2022;**28**:51–64
190. Bhangui P, Yadav S, Soin AS. Post liver transplant recurrence in patients with hepatocellular carcinoma: not necessarily the end of the road!. *Hepatoma Res* 2020;**6**:71
191. Alnagar A, Zakeri N, Koilias K, Faulkes RE, Brown R, Cain O *et al.* SIMAP500: a novel risk score to identify recipients at higher risk of hepatocellular carcinoma recurrence following liver transplantation. *World J Transplant* 2024;**14**:95849